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(54) Title: INHIBITORS OF IMPDH ENZYME

(57) Abstract

The present invention relates to compounds which inhibit IMPDH. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting IMPDH enzyme activity and consequently, may be advantageously used as therapeutic agents for IMPDH mediated processes. This invention also relates to methods for inhibiting the activity of IMPDH using the compounds of this invention and related compounds.

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INHIBITORS OF IMPDH ENZYMETECHNICAL FIELD OF THE INVENTION

The present invention relates to compounds
5 which inhibit IMPDH. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting IMPDH enzyme activity and consequently, may be
10 advantageously used as therapeutic agents for IMPDH mediated processes. This invention also relates to methods for inhibiting the activity of IMPDH using the compounds of this invention and related compounds.

15

BACKGROUND OF THE INVENTION

The synthesis of nucleotides in organisms is required for the cells in those organisms to divide and replicate. Nucleotide synthesis in mammals may be achieved through one of two pathways: the *de novo*
20 synthesis pathway or the salvage pathway. Different cell types use these pathways to a different extent.

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanosine nucleotides. IMPDH catalyzes the
25 NAD-dependent oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) [Jackson R.C. et. al., Nature, 256, pp. 331-333, (1975)].

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IMPDH is ubiquitous in eukaryotes, bacteria and protozoa [Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93 (1993)]. The prokaryotic forms share 30-40% sequence identity with the human enzyme. Regardless of 5 species, the enzyme follows an ordered Bi-Bi reaction sequence of substrate and cofactor binding and product release. First, IMP binds to IMPDH. This is followed by the binding of the cofactor NAD. The reduced cofactor, NADH, is then released from the product, followed by the 10 product, XMP [S.F. Carr et al., J. Biol. Chem., 268, pp. 27286-90 (1993); E.W. Holmes et al., Biochim. Biophys. Acta, 364, pp. 209-217 (1974)]. This mechanism differs 15 from that of most other known NAD-dependent dehydrogenases, which have either a random order of substrate addition or require NAD to bind before the substrate.

Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced [F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-20 15772, (1988); Y. Natsumeda et. al., J. Biol. Chem., 265, pp. 5292-5295, (1990)]. Each is 514 amino acids, and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit 25 molecular weights of 56 kDa [Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745 (1988)].

The *de novo* synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than salvage pathway to generate sufficient 30 levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen [A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison

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et. al., Ciba Found. Symp., 48, 207, (1977)]. Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

5 Immunosuppression has been achieved by inhibiting a variety of enzymes including for example, the phosphatase calcineurin (inhibited by cyclosporin and FK-506); dihydroorotate dehydrogenase, an enzyme involved in the biosynthesis of pyrimidines (inhibited by
10 leflunomide and brequinar); the kinase FRAP (inhibited by rapamycin); and the heat shock protein hsp70 (inhibited by deoxyspergualin). [See B. D. Kahan, Immunological
Reviews, 136, pp. 29-49 (1993); R. E. Morris, The Journal
of Heart and Lung Transplantation, 12(6), pp. S275-S286
15 (1993)].

Inhibitors of IMPDH are also known. United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 describe mycophenolic acid (MPA) and some of its derivatives as potent, uncompetitive, reversible inhibitors of human
20 IMPDH type I ($K_i=33$ nM) and type II ($K_i=9$ nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen [A. C. Allison et. al., Ann. N. Y.
Acad. Sci., 696, 63, (1993)].

25 Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. [R. E. Morris, Kidney Intl., 49, Suppl. 53, S-26, (1996)]. However, MPA is characterized by undesirable pharmacological properties, such as
30 gastrointestinal toxicity and poor bioavailability. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)].

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Nucleoside analogs such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH [L. Hedstrom, et. al. Biochemistry, 29, pp. 849-854 (1990)]. These compounds, which are competitive inhibitors of IMPDH,
5 suffer from lack of specificity to this enzyme.

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*, was recently approved to prevent acute renal allograft rejection following kidney transplantation. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H. W. Sollinger, Transplantation, 60, pp. 225-232 (1995)]. Several clinical observations, however, limit the therapeutic potential of this drug. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)]. MPA is
10 rapidly metabolized to the inactive glucuronide *in vivo*. [A.C. Allison and E.M. Eugui, Immunological Reviews, 136, pp. 5-28 (1993)]. The glucuronide then undergoes enterohepatic recycling causing accumulation of MPA in the gastrointestinal tract where it cannot exert its
15 IMPDH inhibitory activity on the immune system. This effectively lowers the drug's *in vivo* potency, while increasing its undesirable gastrointestinal side effects.
20

More recently, IMPDH inhibitors of a different class have been described in PCT publication WO 97/40028.

25 It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumor cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy [M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991)]. IMPDH has also been shown to play a
30 role in the proliferation of smooth muscle cells,

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indicating that inhibitors of IMPDH, such as MPA or rapamycin, may be useful in preventing restenosis or other hyperproliferative vascular diseases [C. R. Gregory et al., Transplantation, 59, pp. 655-61 (1995); PCT 5 publication WO 94/12184; and PCT publication WO 94/01105].

Additionally, IMPDH has been shown to play a role in viral replication in some viral cell lines. [S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290 (1993)].
10 Analogous to lymphocyte and tumor cell lines, the implication is that the *de novo*, rather than the salvage, pathway is critical in the process of viral replication.
Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties.
15 Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-vascular hyperproliferative agents, anti-inflammatory agents, antifungal agents, antipsoriatic and anti-viral agents.

20

SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of IMPDH. These compounds can be used alone or in combination with other therapeutic or 25 prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics, and immunosuppressants for the treatment or prophylaxis of transplant rejection and autoimmune disease.

Additionally, these compounds are useful, alone 30 or in combination with other agents, as therapeutic and prophylactic agents for antiviral, anti-tumor, anti-cancer, anti-inflammatory agents, antifungal agents,

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antipsoriatic immunosuppressive chemotherapy and restenosis therapy regimens.

The invention also provides pharmaceutical compositions comprising the compounds of this invention, 5 as well as multi-component compositions comprising additional IMPDH compounds together with an immunosuppressant. The invention also provides methods of using the compounds of this invention, as well as other related compounds, for the inhibition of IMPDH.

10

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the 15 following abbreviations are used:

| | <u>Designation</u> | <u>Reagent or Fragment</u> |
|----|--------------------|---|
| | Ac | acetyl |
| | Me | methyl |
| | Et | ethyl |
| 20 | Bn | benzyl |
| | CDI | carbonyldiimidazole |
| | DIEA | diisopropylethylamine |
| | DMAP | dimethylaminopyridine |
| | DMF | dimethylformamide |
| 25 | DMSO | dimethylsulfoxide |
| | EDC | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| | EtOAc | ethyl acetate |
| | THF | tetrahydrofuran |

30

The following terms are employed herein:

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Unless expressly stated to the contrary, the terms "-SO₂-" and "-S(O)₂-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

5

The terms "halo" or "halogen" refer to a radical of fluorine, chlorine, bromine or iodine.

10

The term "immunosuppressant" refers to a compound or drug which possesses immune response inhibitory activity. Examples of such agents include cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.

15

The term "interferon" refers to all forms of interferons, including but not limited to alpha, beta and gamma forms.

20

IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease. Examples of IMPDH-mediated disease include transplant rejection and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory diseases, cancer, viral replication diseases and vascular diseases.

25

For example, the compounds, compositions and methods of using them of this invention may be used in the treatment of transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, diabetes,

30

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mellitus myasthenia gravis, psoriasis, dermatitis,
eczema, seborrhea, pulmonary inflammation, eye uveitis,
hepatitis, Grave's disease, Hashimoto's thyroiditis,
Behcet's or Sjorgen's syndrome (dry eyes/mouth),
5 pernicious or immunohaemolytic anaemia, idiopathic
adrenal insufficiency, polyglandular autoimmune syndrome,
and glomerulonephritis, scleroderma, lichen planus,
viteligo (depigmentation of the skin), autoimmune
thyroiditis, and alveolitis, inflammatory diseases such
10 as osteoarthritis, acute pancreatitis, chronic
pancreatitis, asthma and adult respiratory distress
syndrome, as well as in the treatment of cancer and
tumors, such as solid tumors, lymphomas and leukemia,
vascular diseases, such as restenosis, stenosis and
15 atherosclerosis, and DNA and RNA viral replication
diseases, such as retroviral diseases, and herpes.

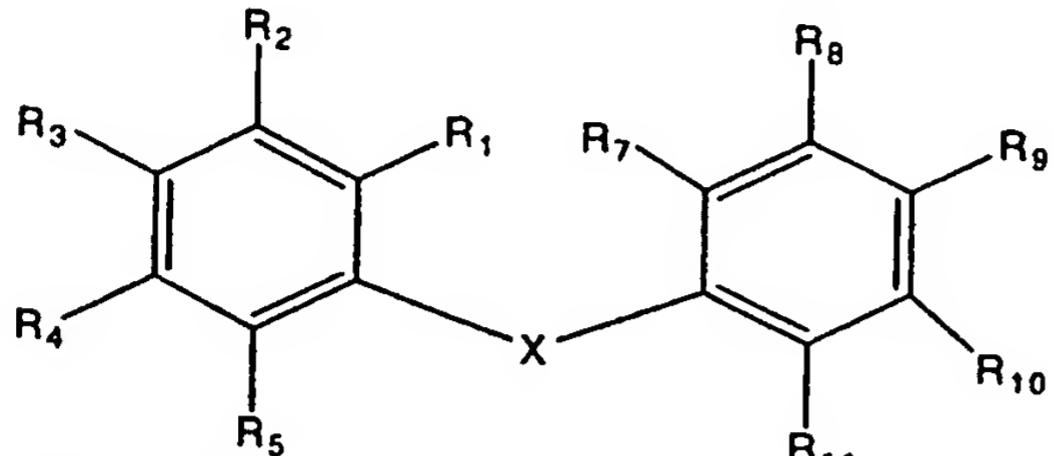
Additionally, IMPDH enzymes are also known to
be present in bacteria and thus may regulate bacterial
growth. As such, the IMPDH-inhibitor compounds,
20 compositions and methods described herein may be useful
in treatment or prevention of bacterial infection, alone
or in combination with other antibiotic agents.

The term "treating" as used herein refers to
the alleviation of symptoms of a particular disorder in a
25 patient or the improvement of an ascertainable
measurement associated with a particular disorder. As
used herein, the term "patient" refers to a mammal,
including a human.

The terms "HBV", "HCV" and "HGV" refer to
30 hepatitis-B virus, hepatitis-C virus and hepatitis-G
virus, respectively.

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According to one embodiment, the invention provides compounds of formula I:



wherein:

X is selected from $-C(O)-N(R_6)-$, $-N(R_6)-C(O)-$, $-CH_2-$
 5 $N(R_6)-$, $-N(R_6)-CH_2-$, $-N(R_6)-S(O)_2-$, $-S(O)_2-N(R_6)-$,
 $-C(R_{12})(R_{12})-C(O)-$, $-C(O)-C(R_{12})(R_{12})-$, $-C(R_{12})(R_{12})-S(O)_2-$,
 $-S(O)_2-C(R_{12})(R_{12})-$, $-S(O)_2-O-$, $-O-S(O)_2-$, $-NR_6-C(O)-Y-$ or
 $Y-C(O)-NR_6-$; wherein

each R_6 is independently selected from hydrogen, C_1-
 10 C_4 straight or branched alkyl, C_2-C_4 straight or branched alkenyl or alkynyl, Ar-substituted- C_1-C_4 straight or branched alkyl, or Ar-substituted- C_2-C_4 straight or branched alkenyl or alkynyl; wherein

R_6 is optionally substituted with up to 3
 15 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

each R_{12} is independently selected from R_6 , $W-[C_1-C_4]$ straight or branched alkyl, $W-[C_2-C_4]$ straight or branched alkenyl or alkynyl, Ar-substituted-[$W-[C_1-C_4]$ straight or
 20 branched alkyl], Ar-substituted-[$W-[C_2-C_4]$ straight or branched alkenyl or alkynyl]], O-Ar, $N(R_6)-Ar$, S-Ar, $S(O)-Ar$, $S(O)_2-Ar$, $S-C(O)H$, $N(R_6)-C(O)H$, or $O-C(O)H$; wherein

W is $O-$, $O-C(O)-$, $S-$, $S(O)-$, $S(O)_2-$, $S-C(O)-$, $N(R_6)-$, or $N(R_6)-C(O)-$; and wherein

25 each R_{12} is optionally and independently substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino.

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and

- Y is selected from $-O-$, $-S-$, $-C\equiv C-$, $-C(R_{12})_2-C(R_{12})_2-$,
 $-C(R_{12})_2-$ or $-C(R_{12})=C(R_{12})-$; wherein
each of R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} and R_{11} is
5 independently selected from hydrogen, halo, hydroxy,
cyano, nitro, amino, $-C(O)NH_2$, $Z-[(C_1-C_4)-$ straight or
branched alkyl], $Z-[(C_2-C_4)-$ straight or branched alkenyl
or alkynyl], Ar-substituted- $[(C_1-C_4)-$ straight or branched
alkyl], Ar-substituted- $[(C_2-C_4)-$ straight or branched
10 alkenyl or alkynyl], Ar, Q-Ar, $[(C_1-C_4)-$ straight or
branched alkyl]-Q-Ar, $[(C_2-C_4)-$ straight or branched
alkenyl or alkynyl]-Q-Ar, $O-[(C_1-C_4)-$ straight or branched
alkyl]-Q-Ar, $O-[(C_2-C_4)-$ straight or branched alkenyl or
alkynyl]-Q-Ar, $[C_1-C_4$ straight or branched alkyl]-Q-R₁₃,
15 $[C_2-C_4$ straight or branched alkenyl or alkynyl]-Q-R₁₃,
or any two adjacent R groups may be taken together with
the carbon atoms to which they are bound to form a 5 to
6-membered aromatic carbocyclic or heterocyclic ring;
wherein
20 Z is selected from a bond, $O-$, $S-$, $S(O)_2-$, $C(O)-$,
 $OC(O)-$, or $N(H)C(O)-$;
Q is selected from O, $-O-C(O)-$, $-C(O)-O-$,
 $-N(H)-C(O)-O-$, $-O-N(H)-C(O)-$, $-N(H)-C(O)-$, $-C(O)-N(H)-$,
 $-O-C(O)-N(H)-$, or $-C(O)-N(H)-O-$;
25 Ar is selected from phenyl, 1-naphthyl, 2-naphthyl,
indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-
furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-
pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl,
30 isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-
thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-
triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl,

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isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl,
benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl,
benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl,
isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl,
5 cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl,
1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl,
phenazinyl, phenothiazinyl or phenoxazinyl or other
chemically feasible monocyclic, bicyclic or tricyclic
ring systems, wherein each ring consists of 5 to 7 ring
10 atoms and wherein each ring comprises 0 to 3 heteroatoms
independently selected from N, O and S;

R₁₃ is selected from [C₁-C₁₂ straight or branched alkyl] or, [C₂-C₁₂ straight or branched alkenyl or
alkynyl]; wherein R₁₃ is optionally substituted with 1 to
15 4 substituents independently selected from R₁₄ or R₁₅,
wherein

each R₁₄ is a monocyclic or a bicyclic ring system
consisting of 3 to 7 members per ring, wherein said ring
system optionally comprises up to 4 heteroatoms selected
20 from N, O, or S; wherein a CH₂ adjacent to said N, O or S
maybe substituted with C(O); and wherein R₁₄ optionally
comprises up to 2 substituents independently selected
from (C₁-C₄)-straight or branched alkyl, (C₂-C₄) straight
or branched alkenyl, 1,2-methylenedioxy, 1,2-
25 ethylenedioxy, (CH₂)_n-R₁₆, -S-(CH₂)_n-R₁₆, -S(O)-(CH₂)_n-R₁₆,
-S(O)₂-(CH₂)_n-R₁₆, -O-(CH₂)_n-R₁₆, or -N(R₁₈)-(CH₂)_n-R₁₆
wherein n is 0, 1 or 2;

R₁₆ is selected from halogen, -CN, -NO₂, -CF₃, -OCF₃,
-OH, -S-(C₁-C₄)-alkyl, -S(O)-(C₁-C₄)-alkyl, -S(O)₂-(C₁-C₄)-
30 alkyl, -NH₂, -NH-(C₁-C₄)-alkyl, N((C₁-C₄)-alkyl)₂, COOH,
C(O)-O-(C₁-C₄)-alkyl or O-(C₁-C₄)-alkyl; and

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each R₁₅ is independently selected from -OR₁₇, or
-N(R₁₈)₂;

R₁₇ is selected from hydrogen, -(C₁-C₆)-straight alkyl, -(C₁-C₆)-straight alkyl-Ar, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, or -(C₁-C₆)-straight alkyl-CN; and

each R₁₈ is independently selected from -(C₁-C₆)-straight or branched alkyl, -(C₁-C₆)-straight or branched alkyl-Ar, -(C₁-C₆)-straight alkyl-CN, -(C₁-C₆)-straight alkyl-OH, -(C₁-C₆)-straight alkyl-OR₁₇, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, -S(O)₂-(C₁-C₆)-straight or branched alkyl, or -S(O)₂-Ar

any alkyl, alkenyl or alkynyl group is optionally substituted with 1 to 3 independently selected halo groups; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally substituted with 1 to 3 substituents independently selected from halo, hydroxy, nitro, cyano, amino, (C₁-C₄)-straight or branched alkyl; O-(C₁-C₄)-straight or branched alkyl, (C₂-C₄)-straight or branched alkenyl or alkynyl, or O-(C₂-C₄)-straight or branched alkenyl or alkynyl; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally benzofused.

In addition, in these compounds, at least two of R₁, R₂, R₃, R₄, or R₅ is hydrogen;

no more than two of R₁, R₂, R₃, R₄, or R₅ comprises Ar;

at least two of R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen; and no more than two of R₇, R₈, R₉, R₁₀ or R₁₁ comprises Ar.

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The compounds of this invention specifically exclude those wherein X is $-\text{NH}-\text{S}(\text{O})_2-$ or $-\text{S}(\text{O})_2-\text{N}(\text{H})-$, one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is O-(C₁-C₄)-straight or branched alkyl, seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen and the remaining two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are bound together to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring.

Also excluded are compounds wherein X is $-\text{NH}-\text{S}(\text{O})_2-$ or $-\text{S}(\text{O})_2-\text{N}(\text{H})-$, two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are O-(C₁-C₄)-straight or branched alkyl, seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen and the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is $-\text{NO}_2$, $-\text{CN}$ or $-\text{Ar}$.

Another set of compounds excluded from the present invention are those wherein X is $-\text{NH}-\text{S}(\text{O})_2-$ or $-\text{S}(\text{O})_2-\text{N}(\text{H})-$, two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are O-(C₁-C₄)-straight or branched alkyl, six of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen and the remaining two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are both halo.

Yet another set of compounds excluded are those wherein X is $-\text{NH}-\text{S}(\text{O})_2-$ or $-\text{S}(\text{O})_2-\text{N}(\text{H})-$, one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is Ar and the remaining 9 of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are each hydrogen.

Another set of excluded compounds are those wherein X is $-\text{N}(\text{H})-\text{C}(\text{O})-\text{S}-$ or $-\text{S}-\text{C}(\text{O})-\text{N}(\text{H})-$, one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is -OH, eight of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen and the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is halo; and those wherein X is $-\text{N}(\text{H})-\text{C}(\text{O})-\text{S}-$ or $-\text{S}-\text{C}(\text{O})-\text{N}(\text{H})-$, one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is

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-OH, seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is O-(C₁-C₄)-straight or branched alkyl and the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is halo or (C₁-C₄)-straight or branched alkyl.

The above-described exclusions from the compounds of this invention reflect compounds which are commercially available. However, those compounds are not known or suggested to inhibit IMPDH, nor have they ever been known or suggested to be formulated with a pharmaceutically acceptable adjuvant, carrier or excipient. Accordingly, these compounds are not excluded from aspects of this invention which involve any methods or compositions recited below.

The term "heterocyclic ring" as used herein refers to a ring which comprises 1 to 4 heteroatoms independently selected from N, O or S.

The terms "Ar-substituted-(C₁-C₄)-straight or branched alkyl" and "Ar-substituted-(C₂-C₄)-straight or branched alkenyl or alkynyl" denote that one or more Ar groups may be attached to the alkyl, alkenyl or alkynyl chain at any chemically feasible position on the chain, including the termini.

References to "[branched alkyl, alkenyl or alkynyl]-Ar" or "[branched alkyl, alkenyl or alkynyl]-Q-Ar" denote that an "Ar" or "Q-Ar" moiety is attached to one or more terminal ends of the branched alkyl, alkenyl or alkynyl chain.

According to a preferred embodiment X is selected from -C(O)-N(R₆)-, -N(R₆)-C(O)-, -CH₂-N(R₆)-, or -N(R₆)-CH₂- or -N(R₆)-C(O)-Y. More preferably, X is

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$-N(R_6)-C(O)-Y.$

Most preferably X is $-N(R_6)-C(O)-C(R_{12})=C(R_{12})-$.

According to another preferred embodiment, R₁ is selected from H, (C₁-C₄)-straight or branched alkyl, OH, 5 O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano or S-(C₁-C₄)-straight or branched alkyl. In an alternate preferred embodiment, R₁ is H when R₂ is not H.

R₂ is preferably selected from H, (C₁-C₄)-straight or branched alkyl, Ar, O-(C₁-C₄)-straight or 10 branched alkyl, O-Ar, OCF₃, halo, cyano, C(O)NH₂ or S(O)₂-(C₁-C₄)-straight or branched alkyl. More preferably, R₂ is H.

R₃ is preferably selected from H, Ar, cyano, O-(C₁-C₄)-straight or branched alkyl, O-Ar, S-(C₁-C₄)-15 straight or branched alkyl, CF₃ or OCF₃.

In another preferred embodiment, R₄ is selected from H, (C₁-C₄)-straight or branched alkyl, OH, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano or S-(C₁-C₄)-straight or branched alkyl.

20 R₅ is preferably selected from H, (C₁-C₄)-straight or branched alkyl, Ar, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano, C(O)NH₂ or S(O)₂-(C₁-C₄)-straight or branched alkyl. More preferably, R₅ is H.

25 According to another preferred embodiment, R₇ is selected from H, OH, OC(O)-(C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, O-Ar, amino, or N(H)C(O)-(C₁-C₄)-straight or branched alkyl. Even more preferred is when R₇ is OH.

30 R₈ is preferably H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, or (C₁-C₄)-straight or branched alkyl-N(H)C(O)O-Ar.

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According to another preferred embodiment, R₉ is selected from H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, or R₉ is taken together with R₁₀ and the carbon atoms to which they are bound to form a fused benzene ring. More preferred is when R₉ and R₁₀ are taken together with the carbon atoms to which they are bound to form a fused benzene ring.

According to a further preferred embodiment, R₁₀ is selected from H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, or R₁₀ is taken together with R₉ and the carbon atoms to which they are bound to form a fused benzene ring.

In another preferred embodiment, R₁₁ is selected from H, OH, OC(O)-(C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, O-Ar, amino, or N(H)C(O)-(C₁-C₄)-straight or branched alkyl. More preferably, R₁₁ is H.

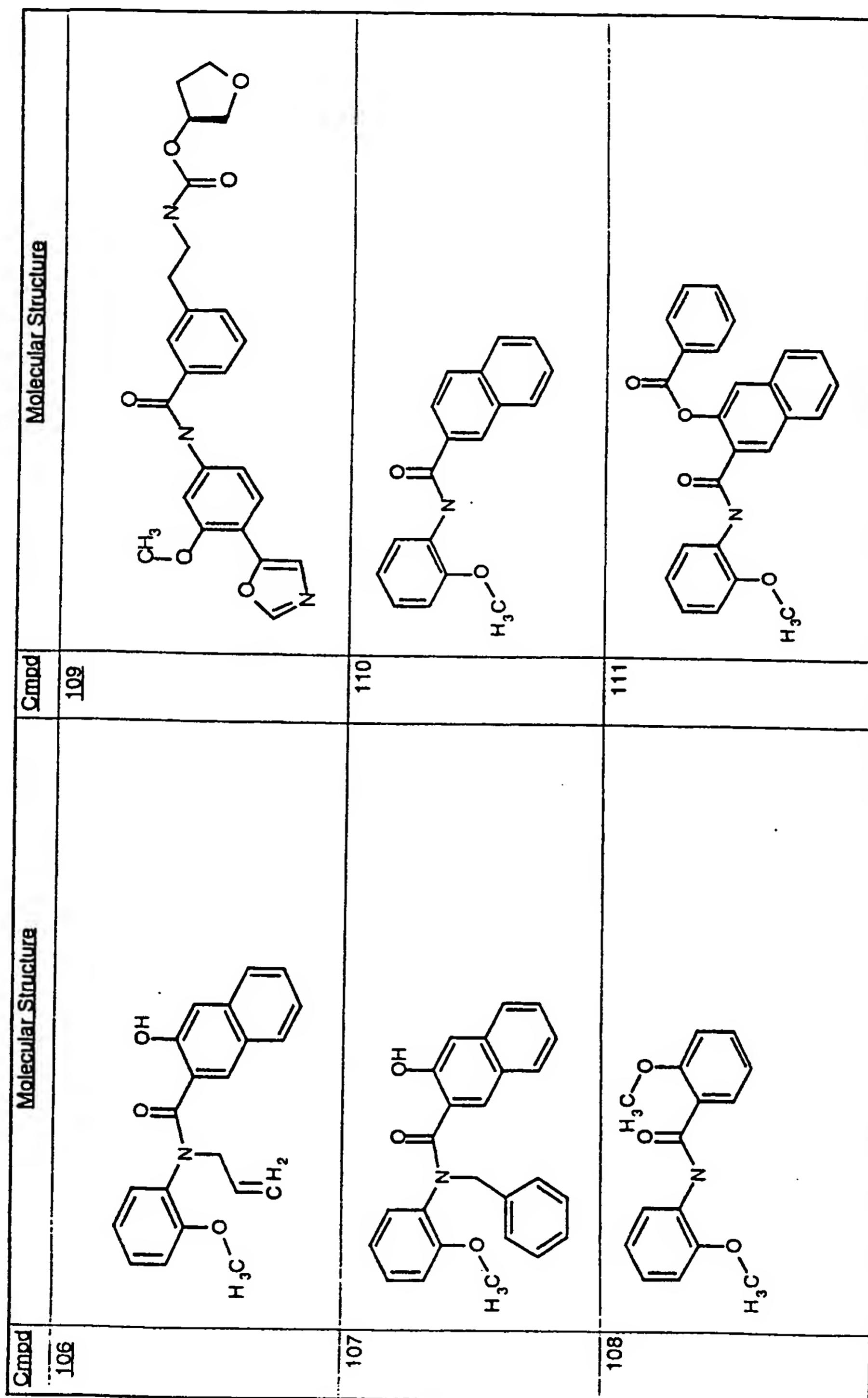
In yet another preferred embodiment, Q is -N(H)-C(O)-O-.

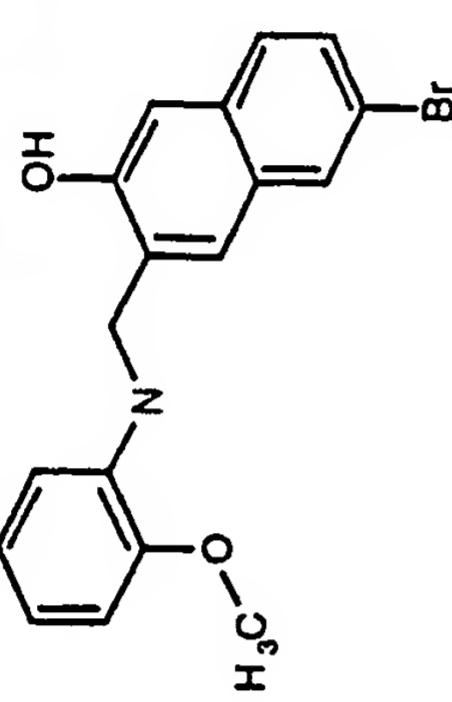
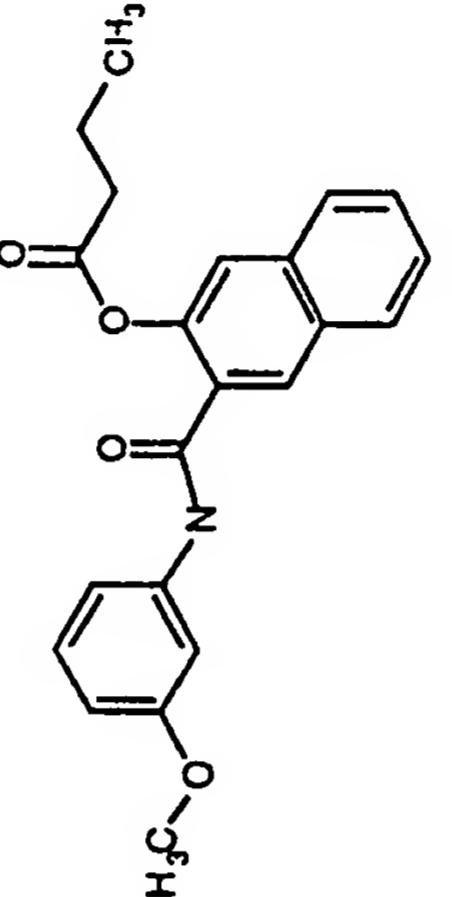
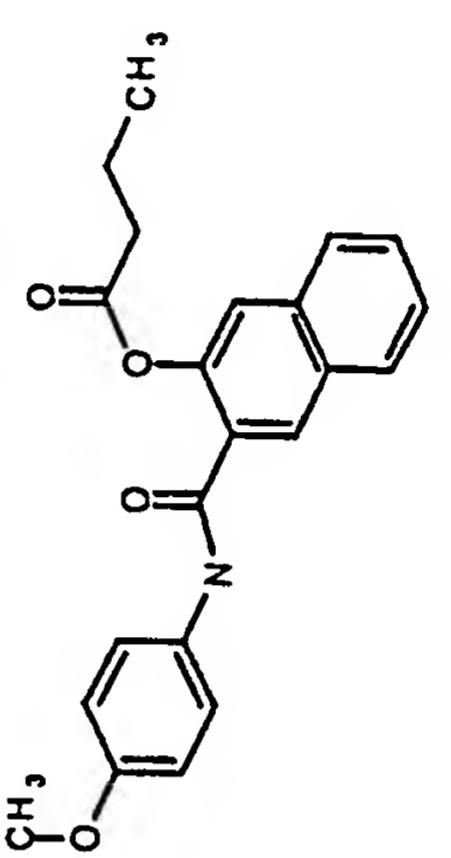
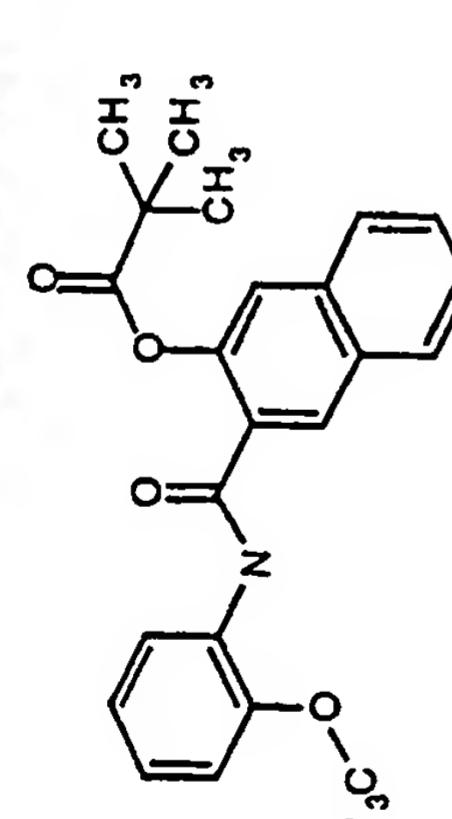
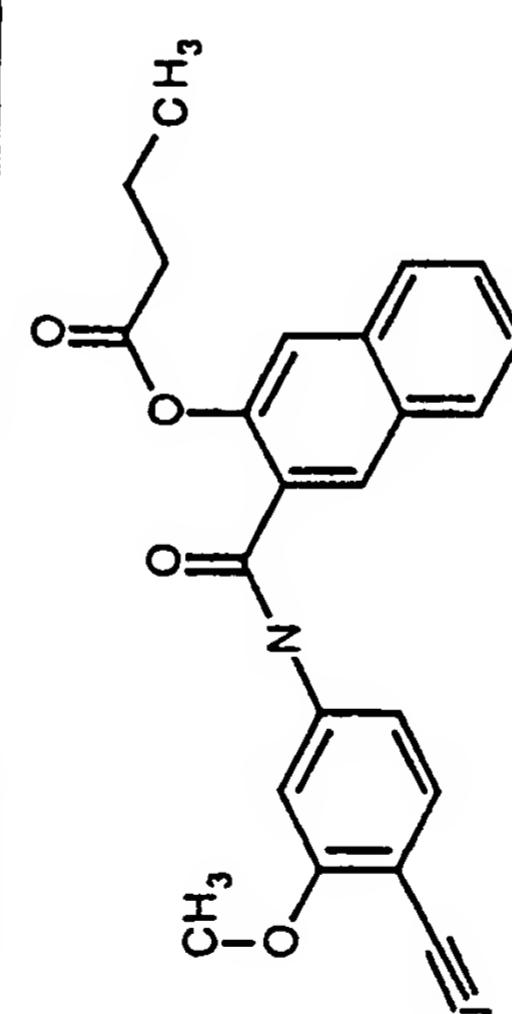
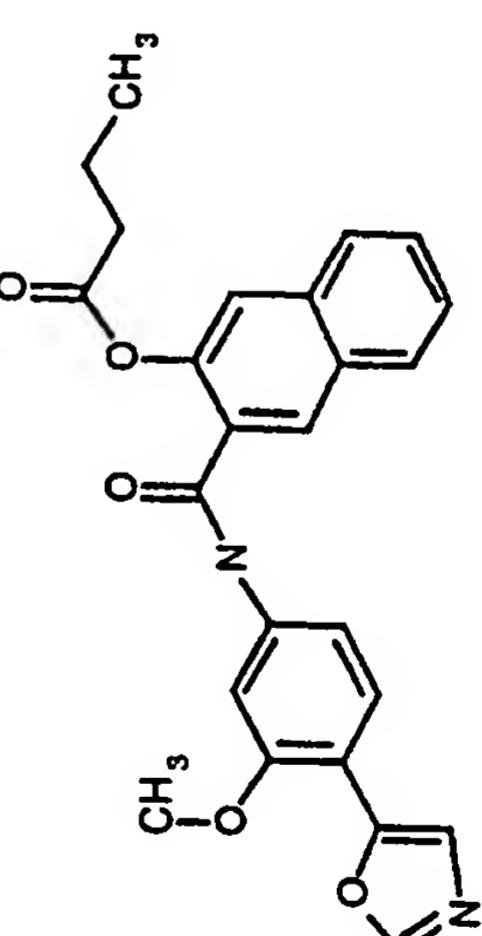
According to another embodiment, preferred compounds of the invention are listed in the table below.

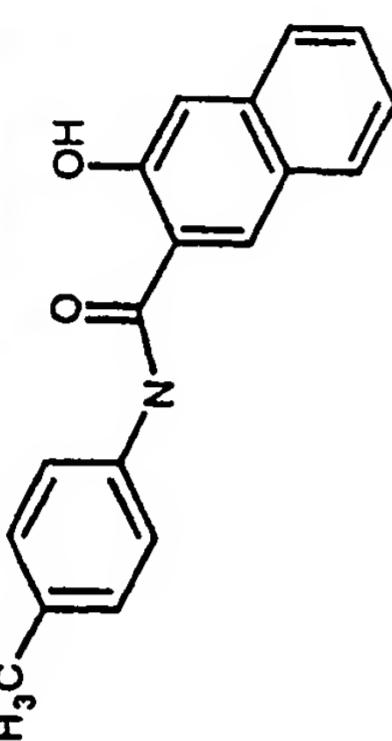
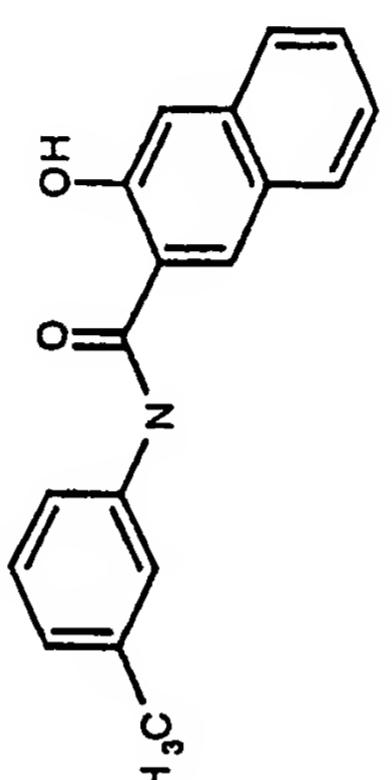
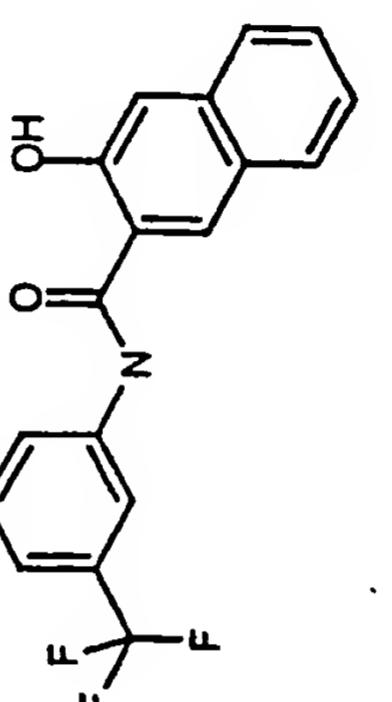
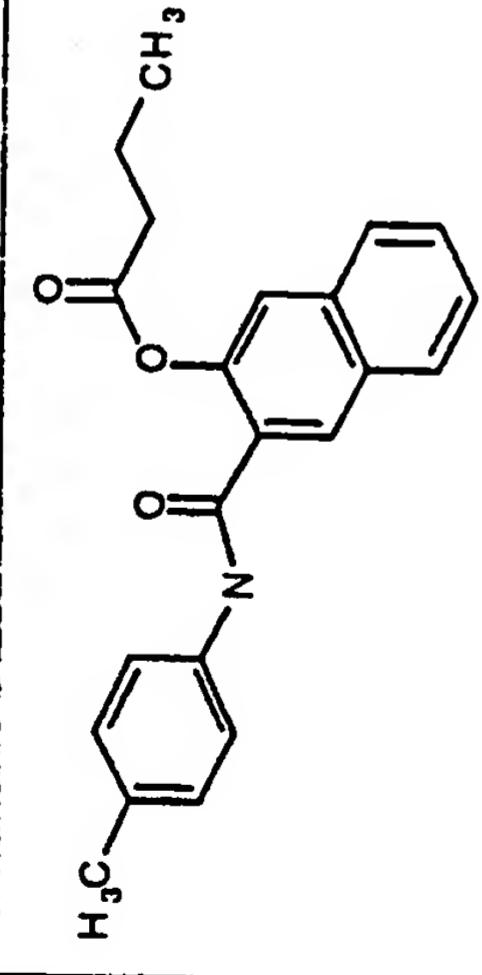
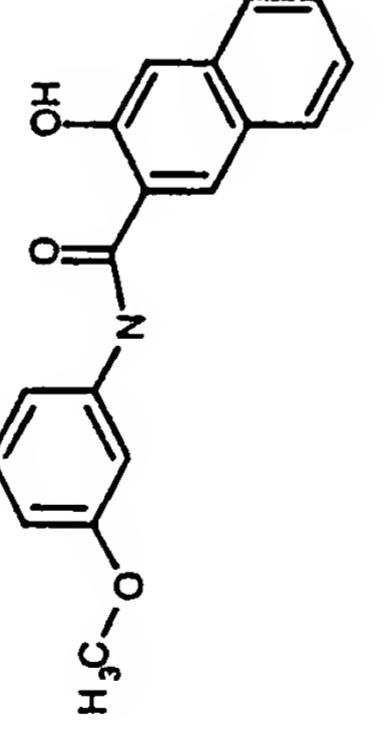
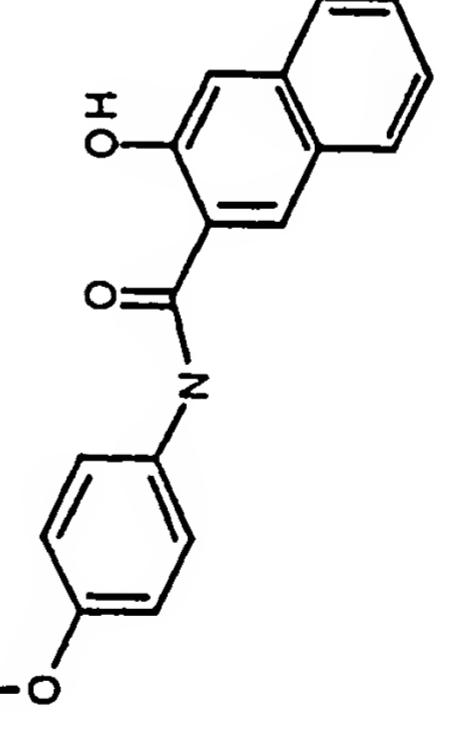
Table 1. Preferred compounds.

| Compd | Molecular Structure | | |
|-------|---------------------|-----|-----|
| | 100 | 101 | 102 |
| 103 | | | |
| 104 | | | |
| 105 | | | |

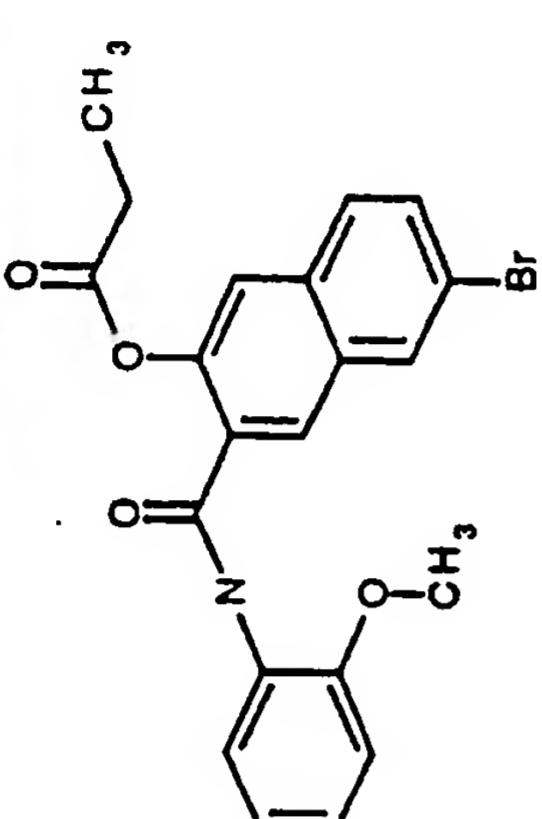
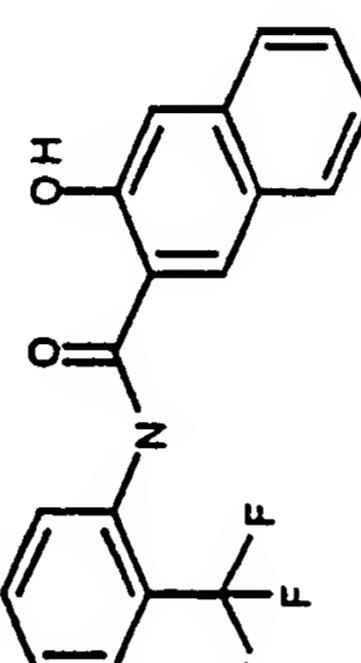
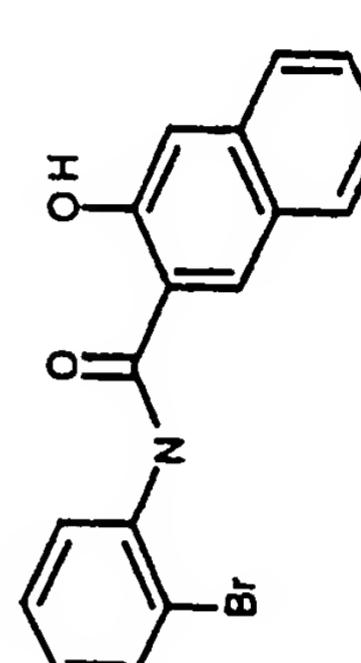
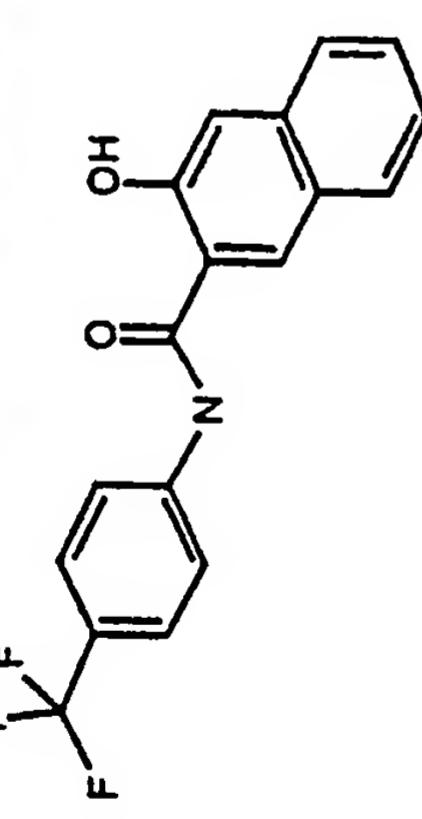
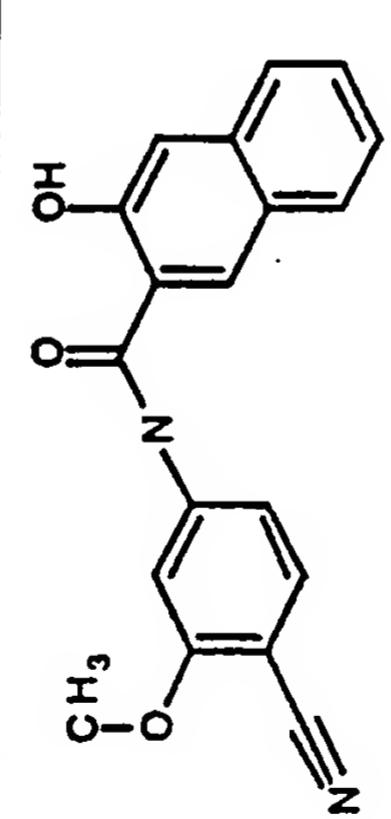
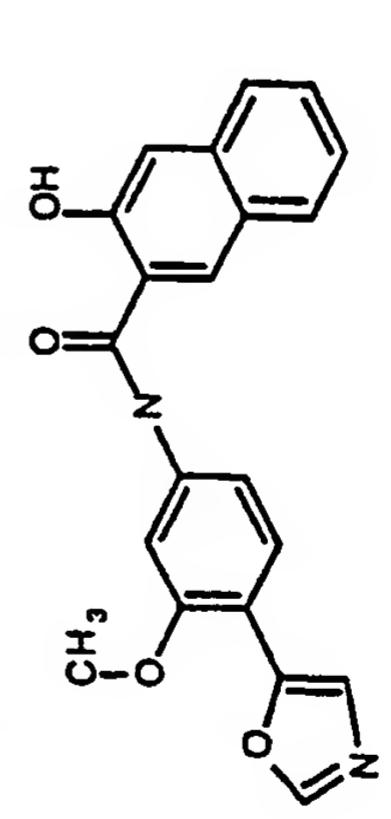
- 18 -



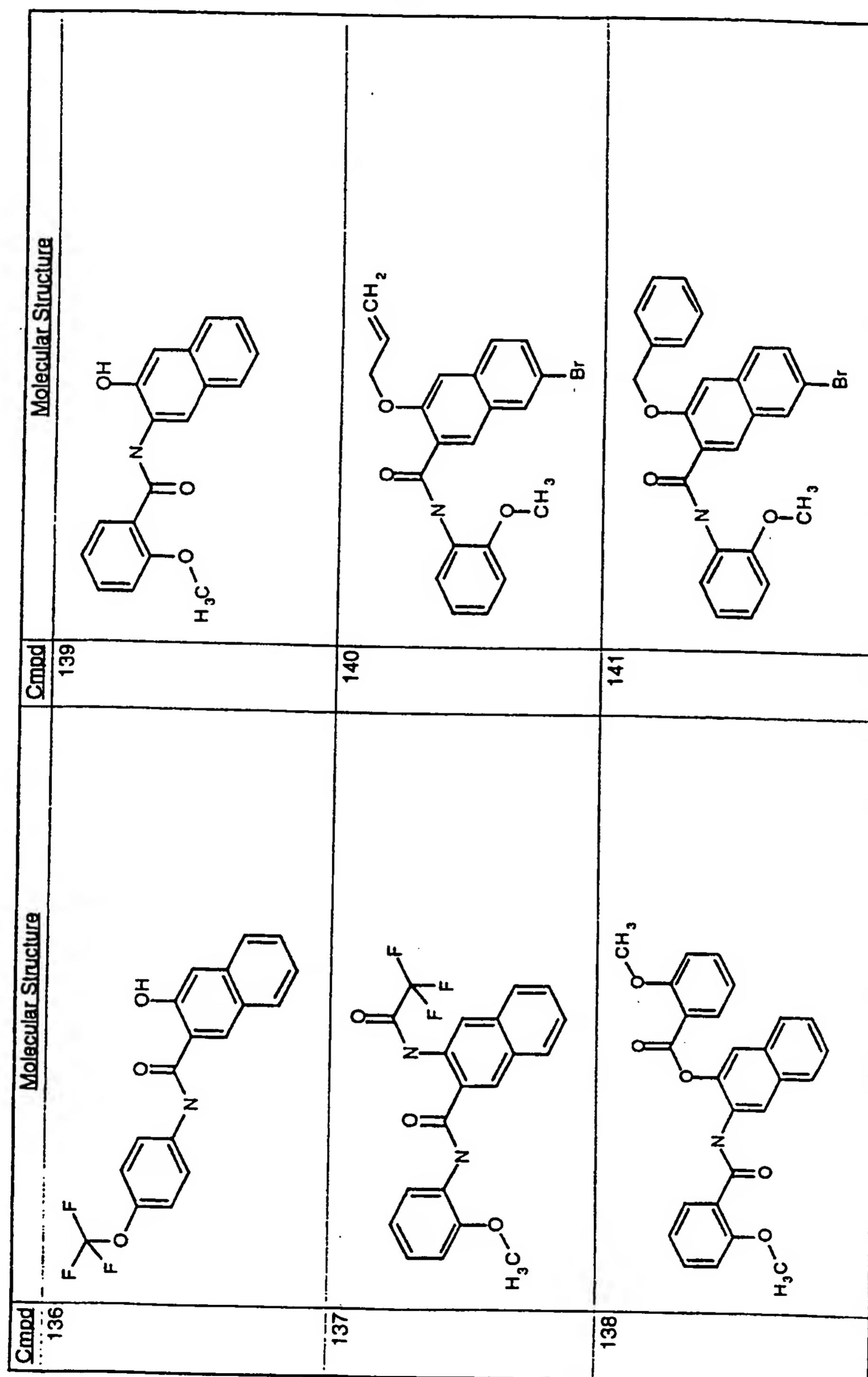
| Molecular Structure | |
|---------------------|---|
| Compd | |
| 115 |  |
| 116 |  |
| 117 |  |
| Compd | |
| 112 |  |
| 113 |  |
| 114 |  |

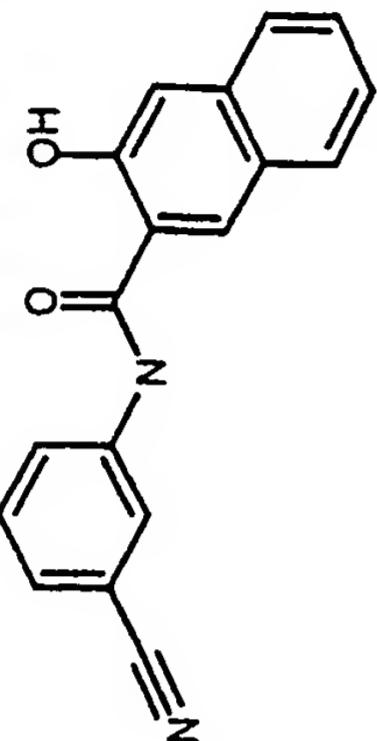
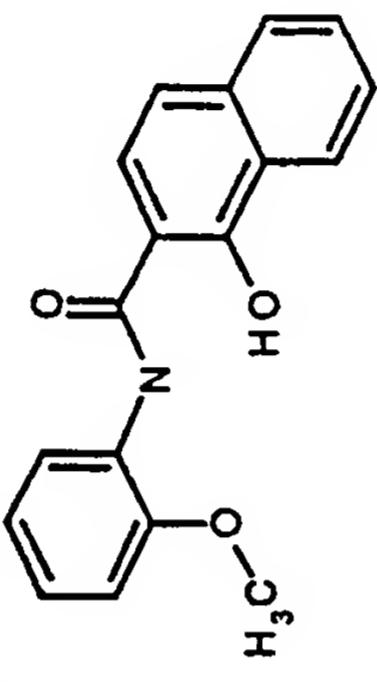
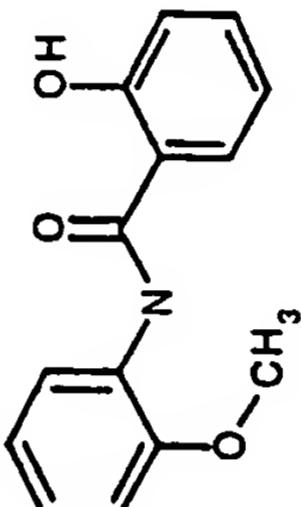
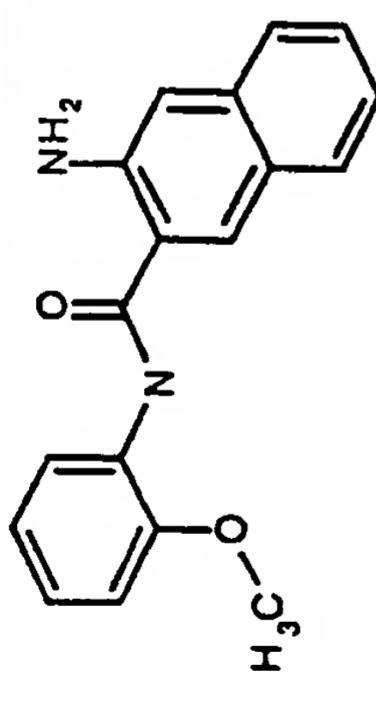
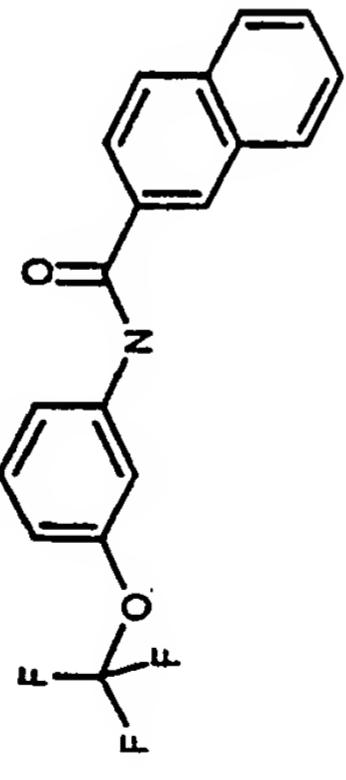
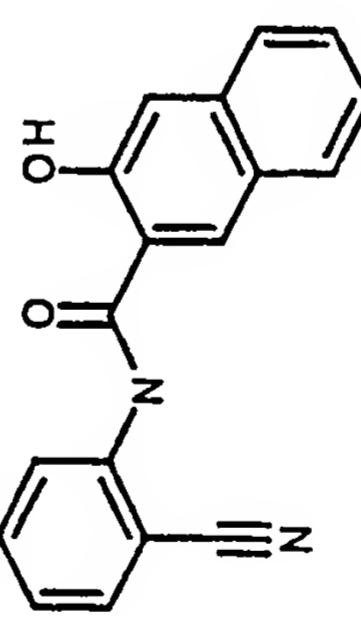
| Molecular Structure | | | |
|---------------------|--|---|---|
| Cmpd | | | |
| 121 |  |  |  |
| Molecular Structure | | | |
| 118 |  |  |  |
| Cmpd | | | |
| 119 | | | |
| 120 | | | |

- 21 -

| | | Molecular Structure | | |
|------|--|---|--|--|
| Cmpd | | | | |
| 127 | |  | | |
| 128 | |  | | |
| 129 | |  | | |
| Cmpd | | Molecular Structure | | |
| 124 | |  | | |
| 125 | |  | | |
| 126 | |  | | |

| Cmpd | Molecular Structure |
|------|---------------------|
| 133 | |
| 134 | |
| 135 | |
| Cmpd | Molecular Structure |
| 130 | |
| 131 | |
| 132 | |

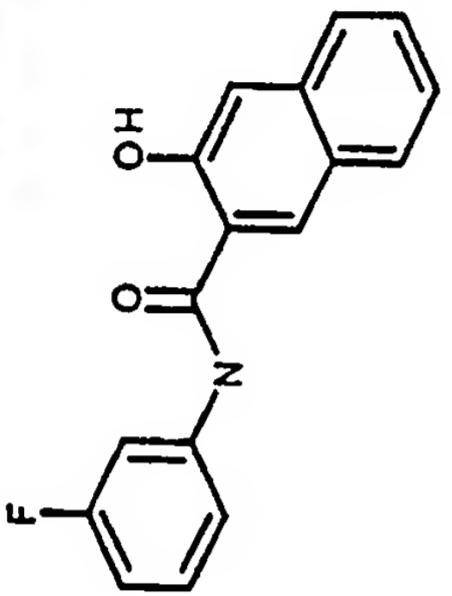
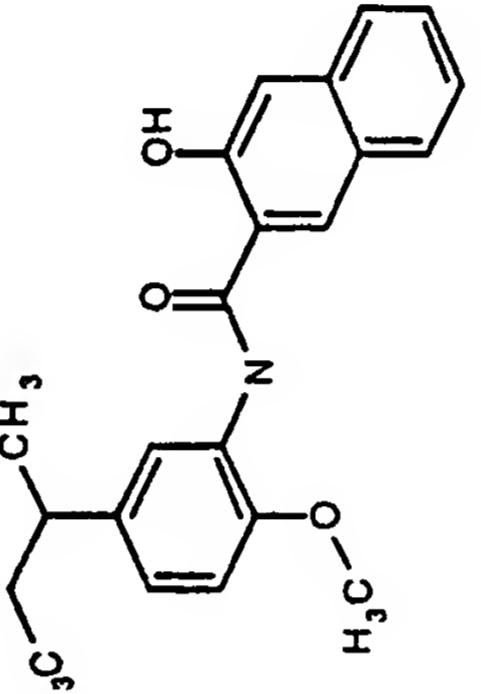
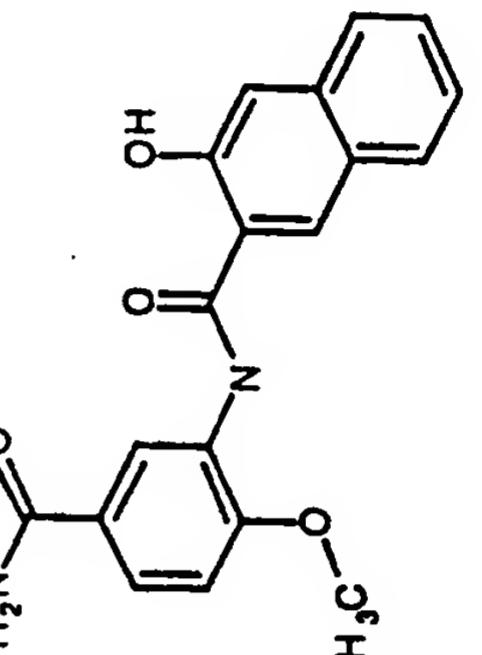
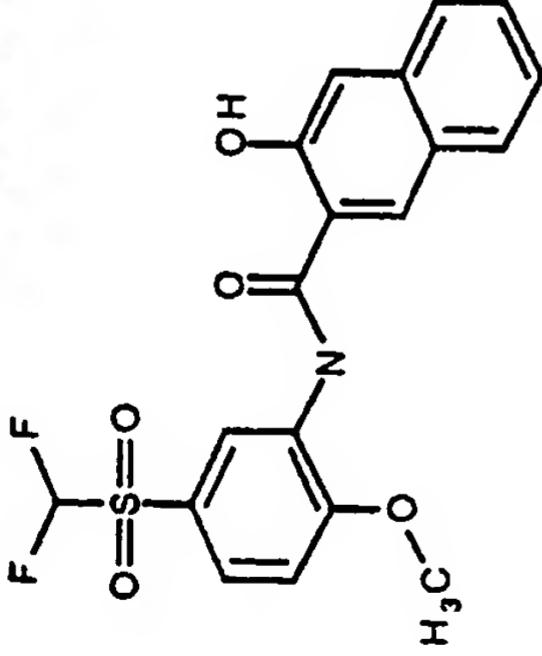
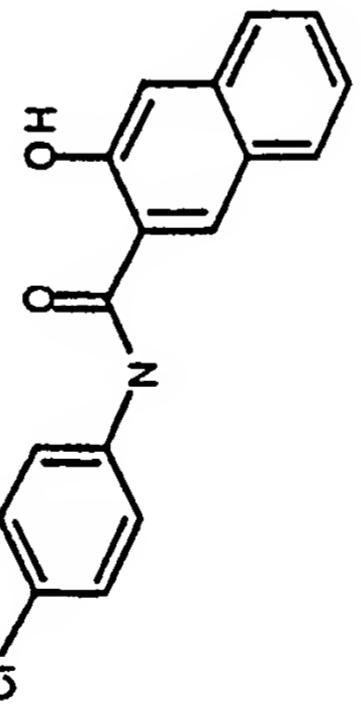
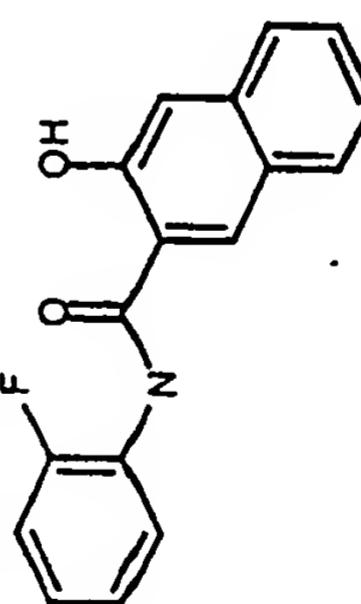


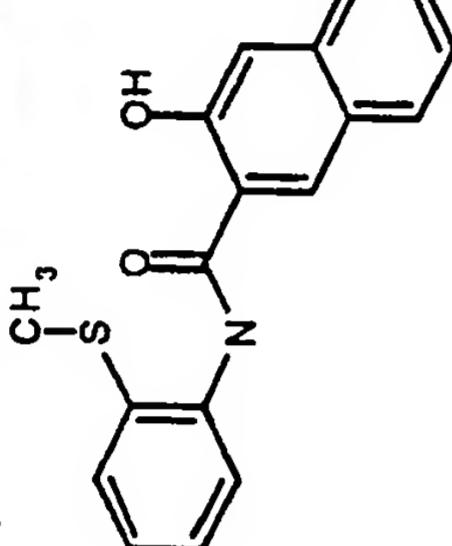
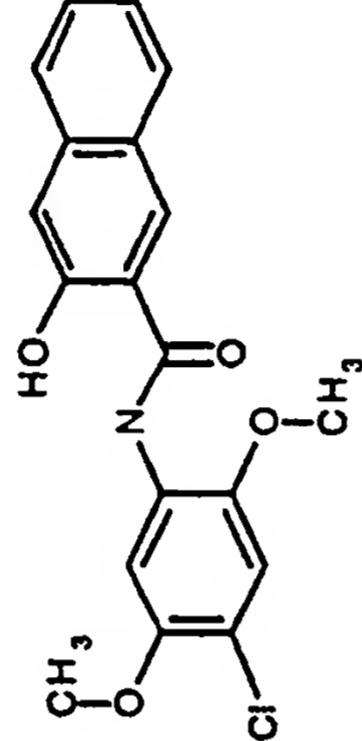
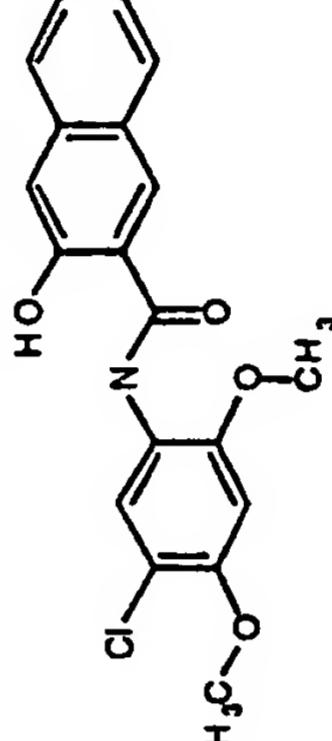
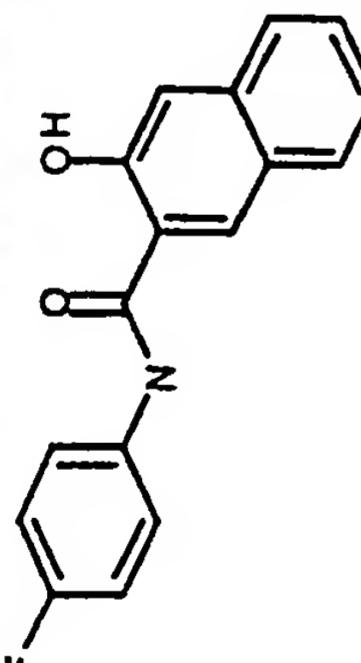
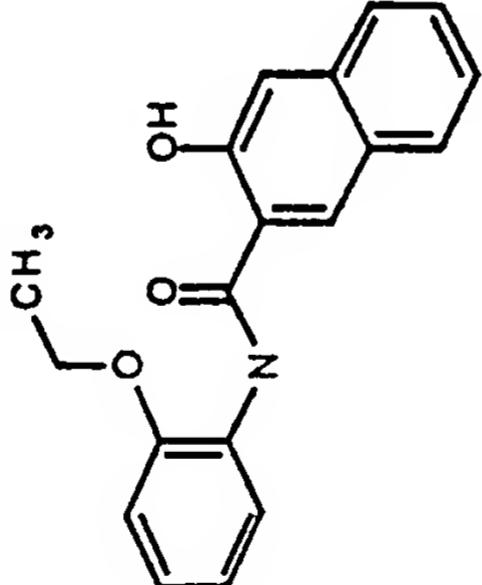
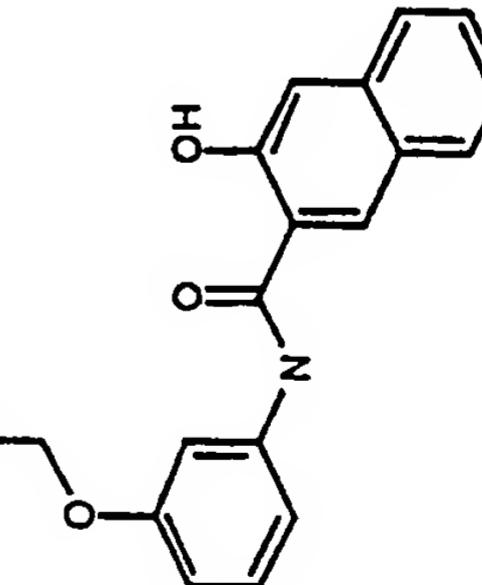
| Cmod | Molecular Structure |
|------|---|
| 145 |  |
| 146 |  |
| 147 |  |
| Cmod | Molecular Structure |
| 142 |  |
| 143 |  |
| 144 |  |

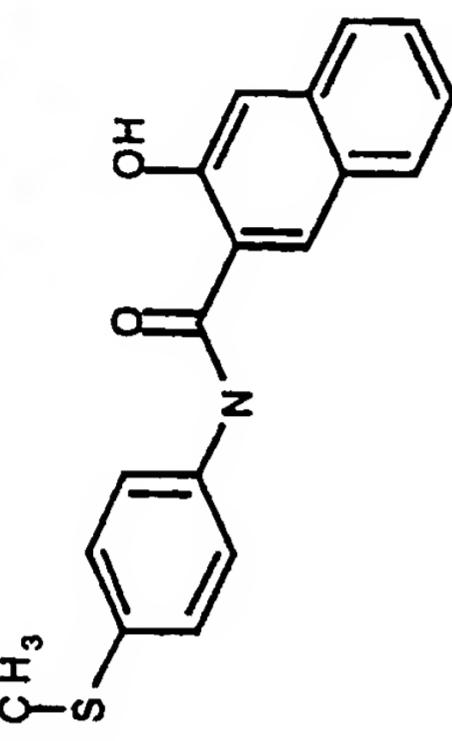
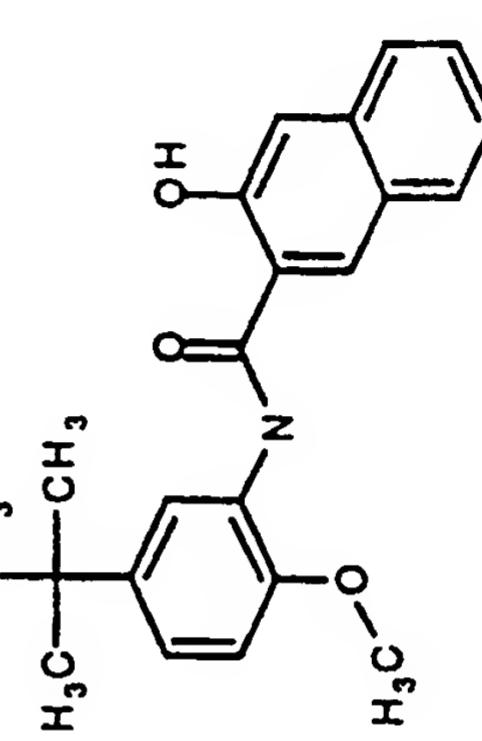
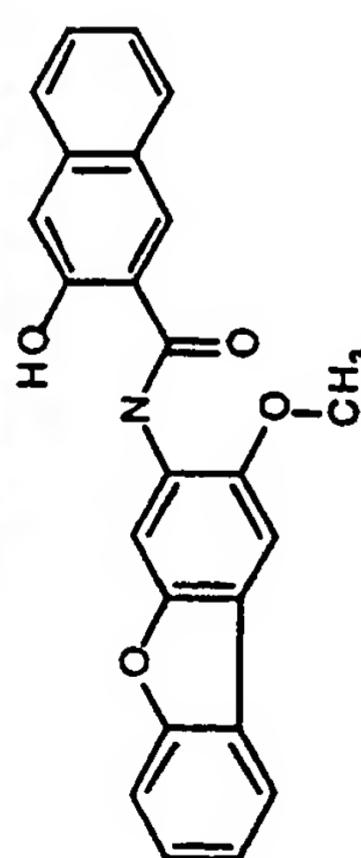
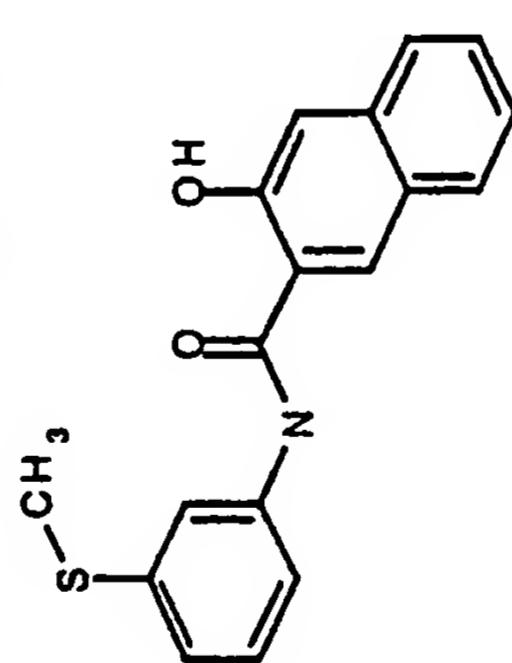
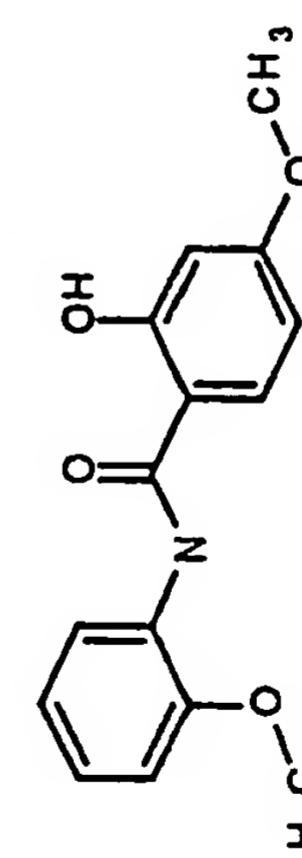
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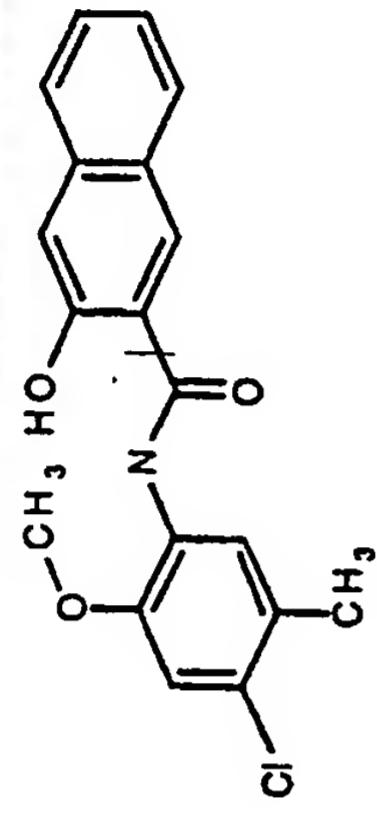
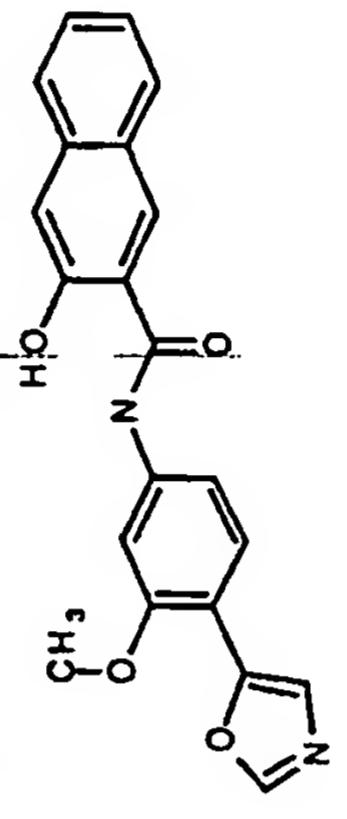
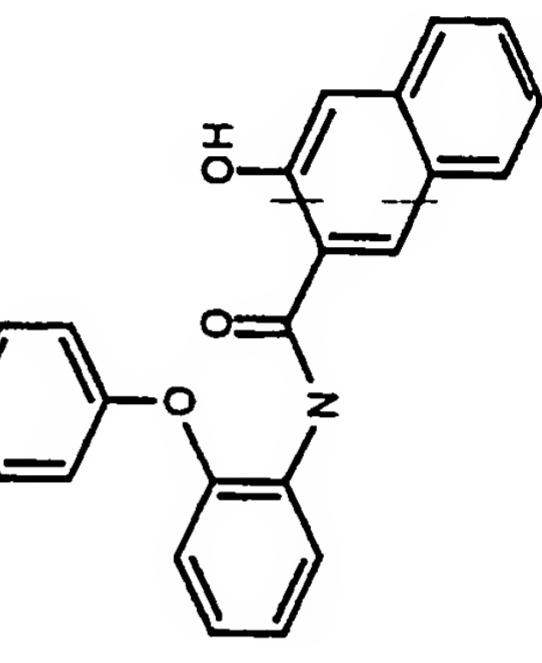
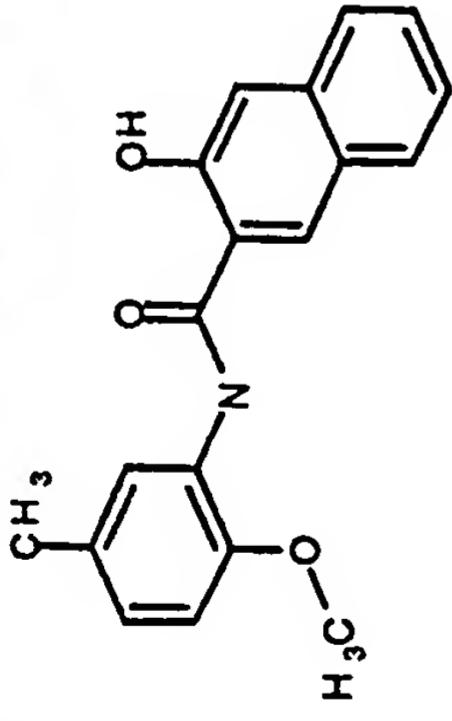
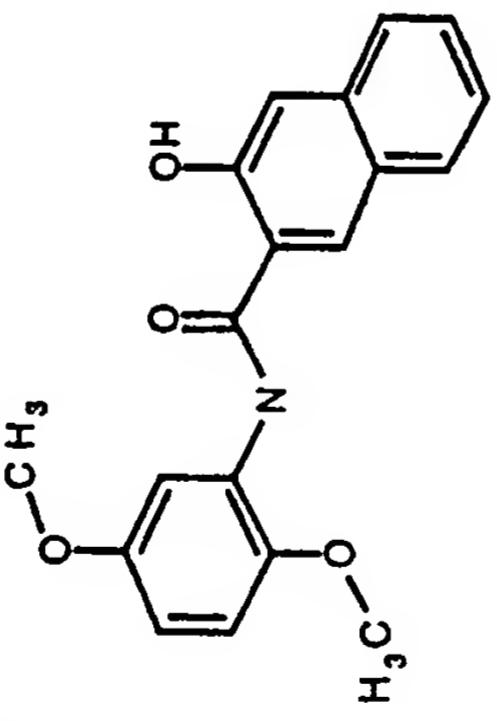
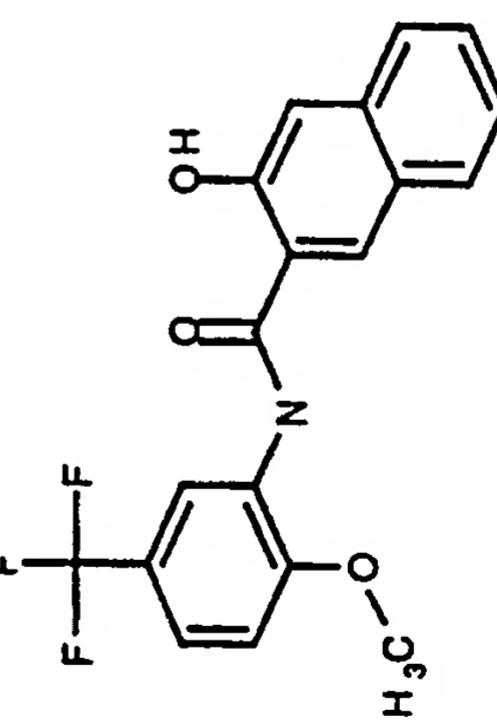
| Compd | Molecular Structure | Compd | Molecular Structure | Compd | Molecular Structure |
|-------|---------------------|-------|---------------------|-------|---------------------|
| 151 | | 152 | | 153 | |
| 148 | | 149 | | 150 | |

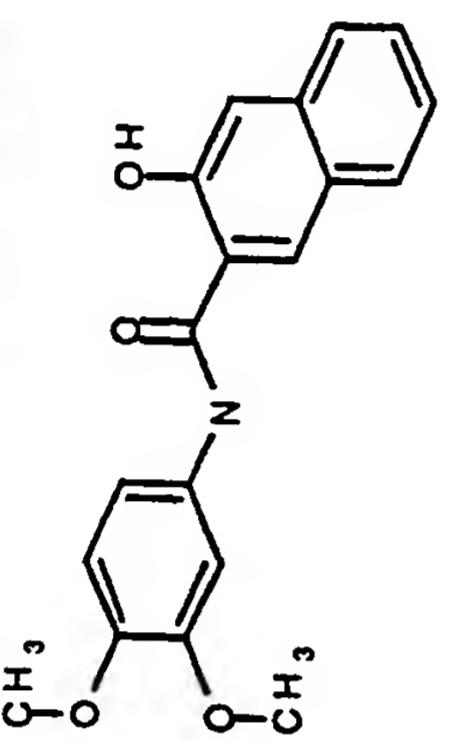
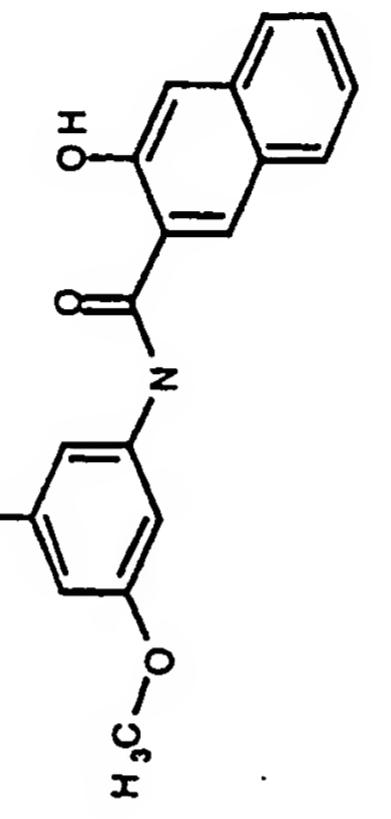
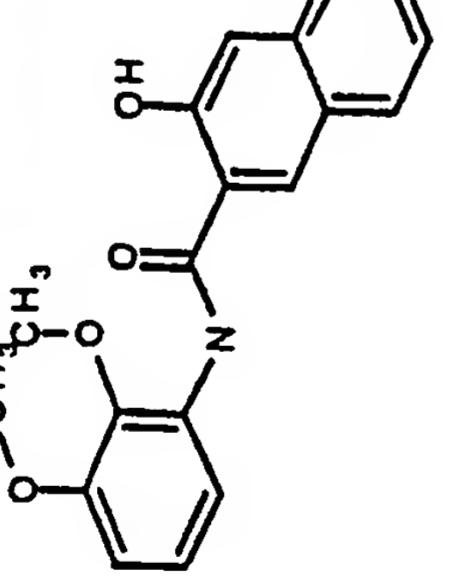
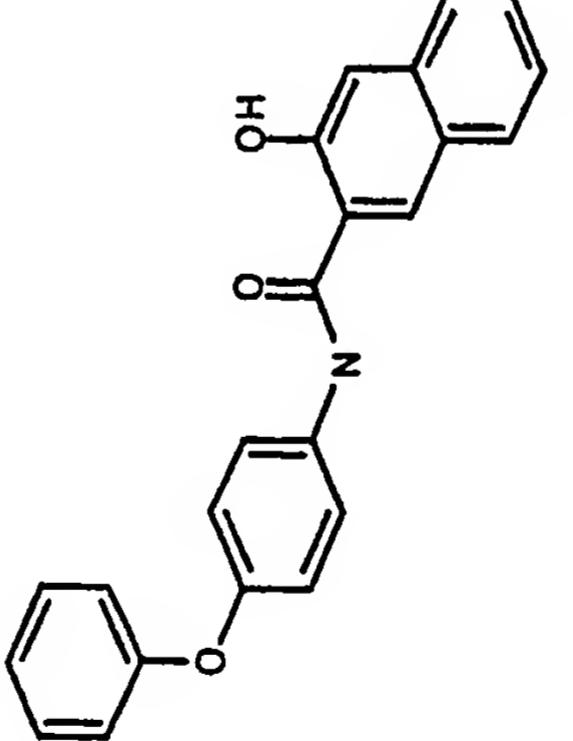
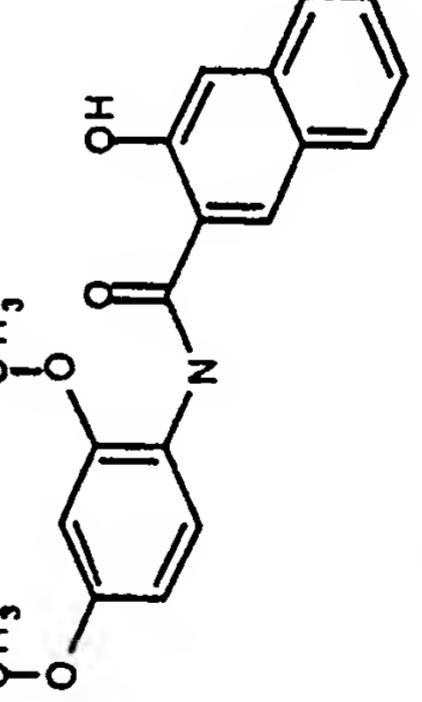
| Molecular Structure | Compd 157 | | Compd 159 |
|---------------------|-----------|-----------|-----------|
| Molecular Structure | Compd 154 | Compd 155 | Compd 156 |
| | | | |
| | | | |

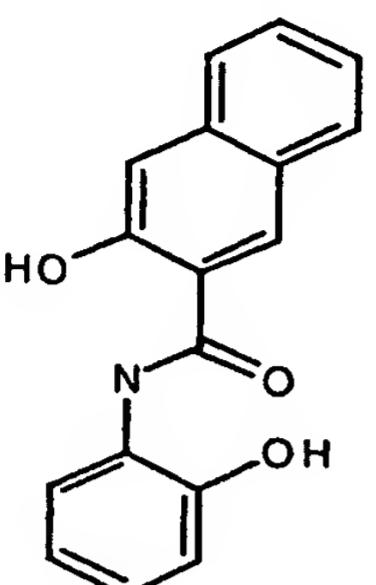
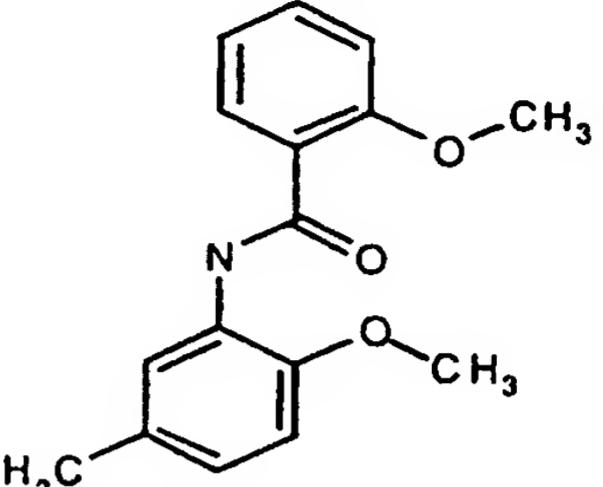
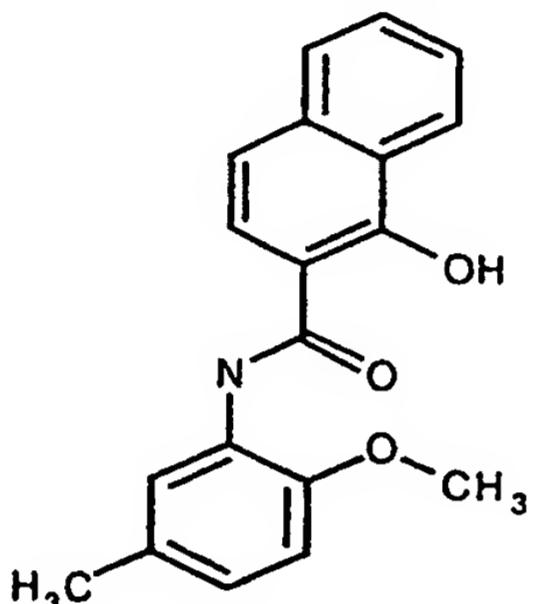
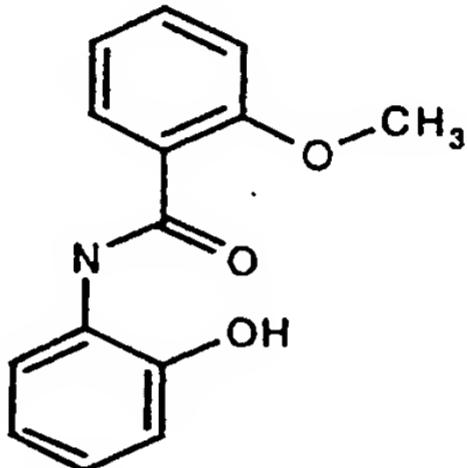
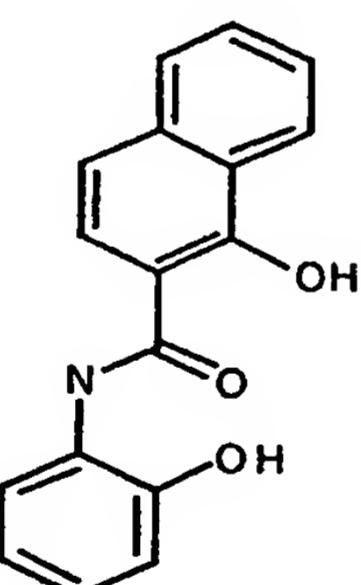
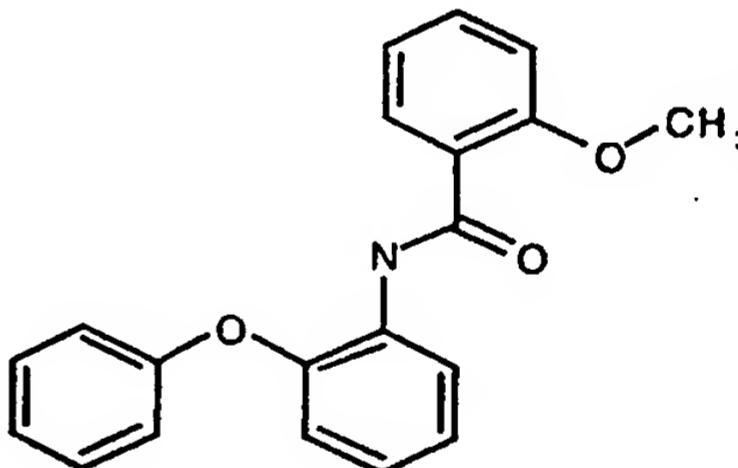
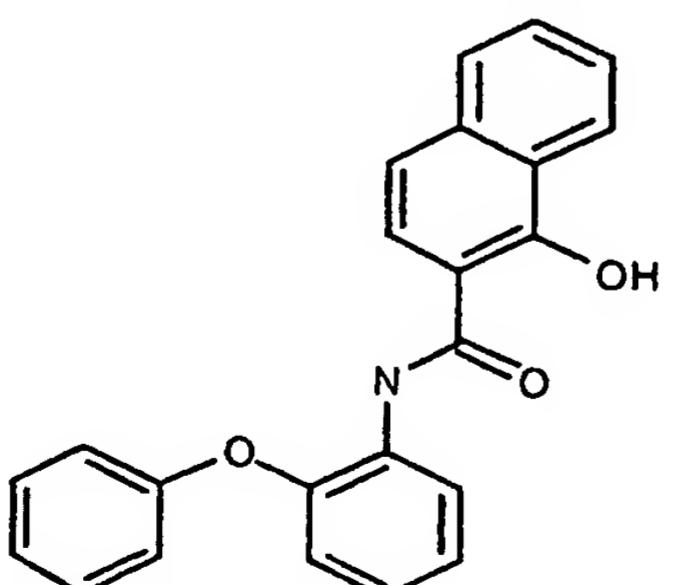
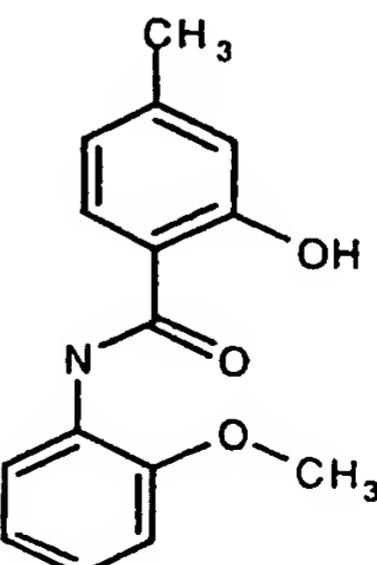
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|---------------------|---|
| Compd | |
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| 164 |  |
| 165 |  |
| Compd | Molecular Structure |
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| 161 |  |
| 162 |  |

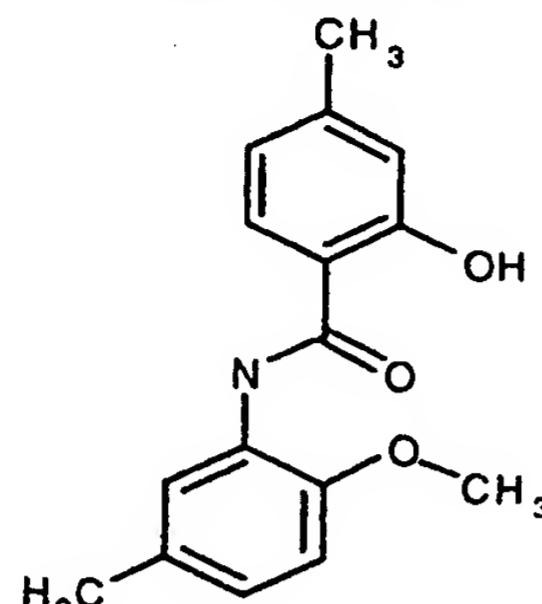
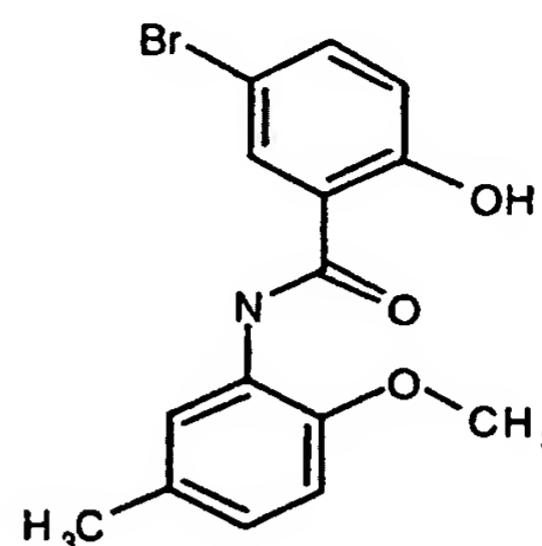
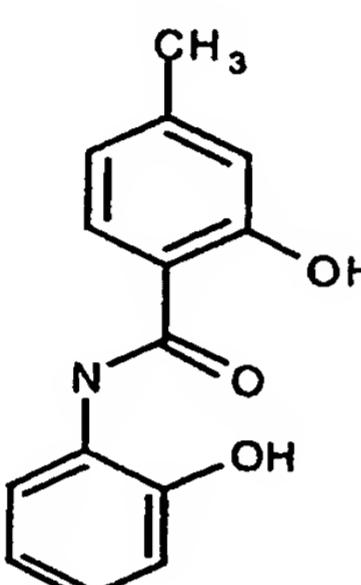
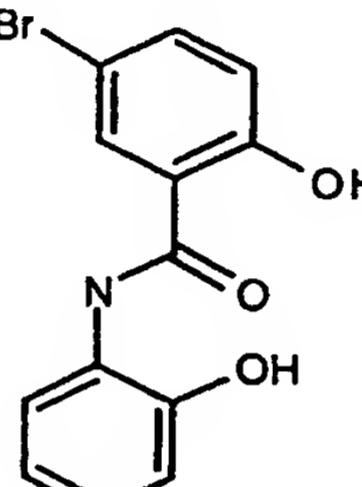
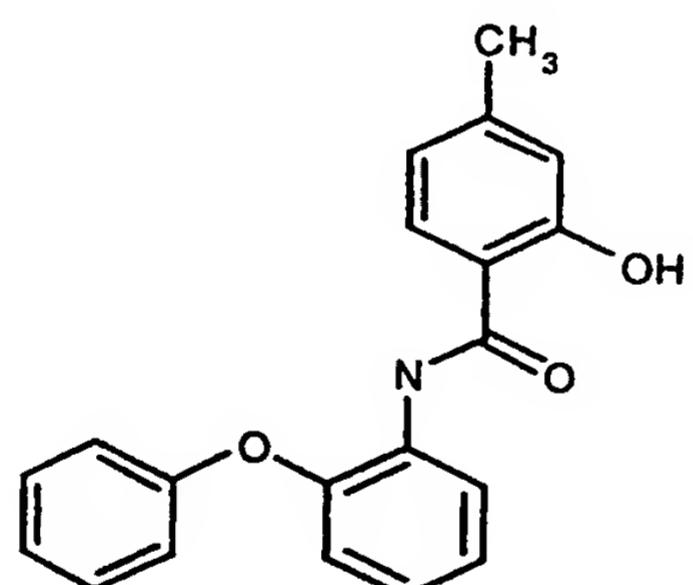
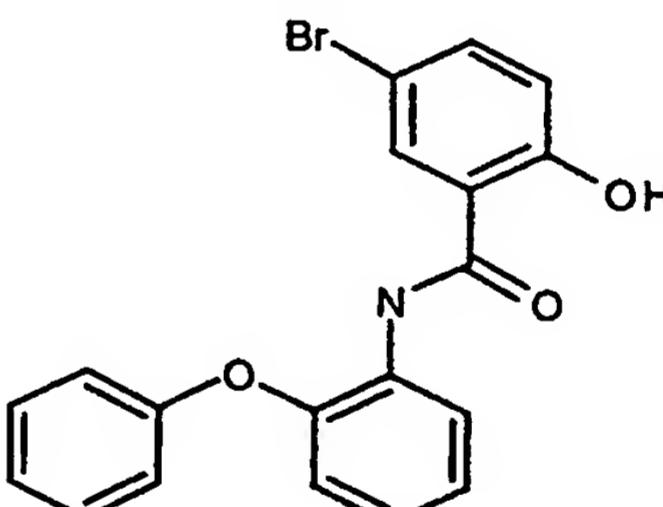
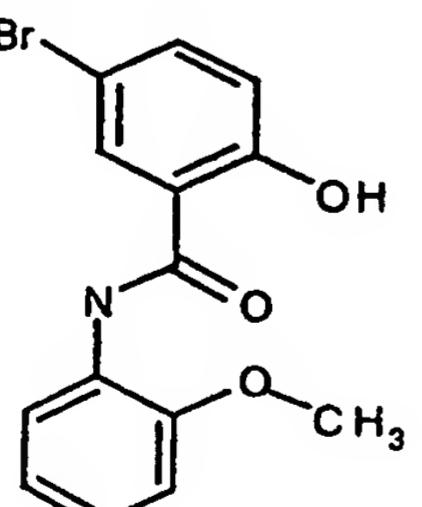
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| 169 |  |  |  |
| Molecular Structure | | | |
| 166 |  |  |  |
| Cmpd | | 167 | 168 |

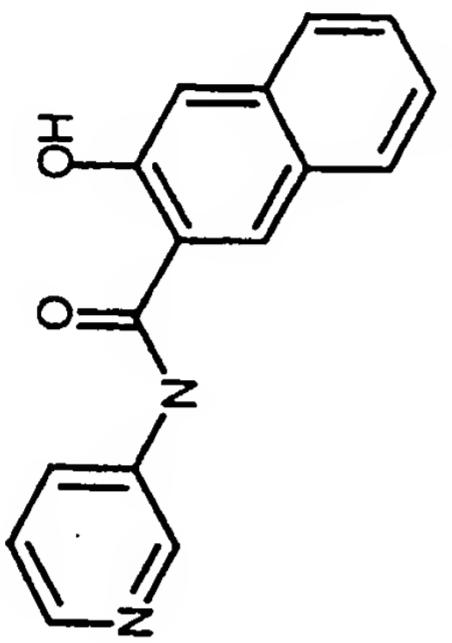
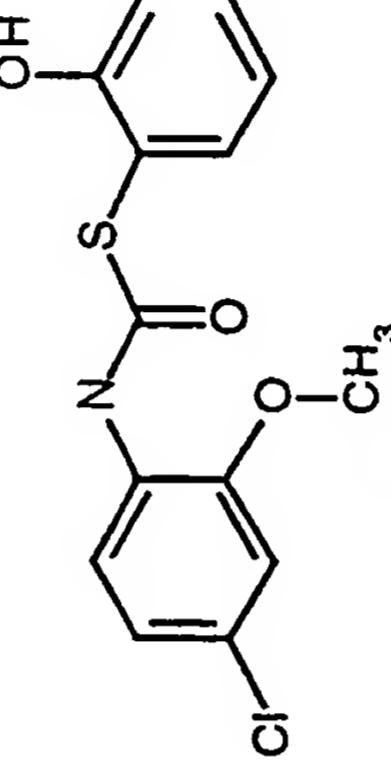
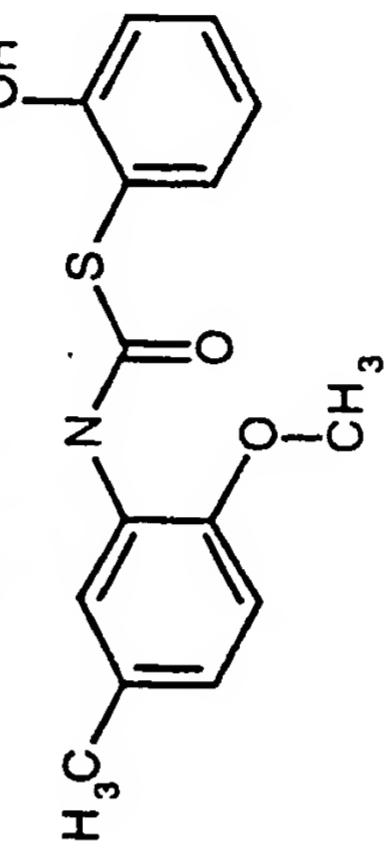
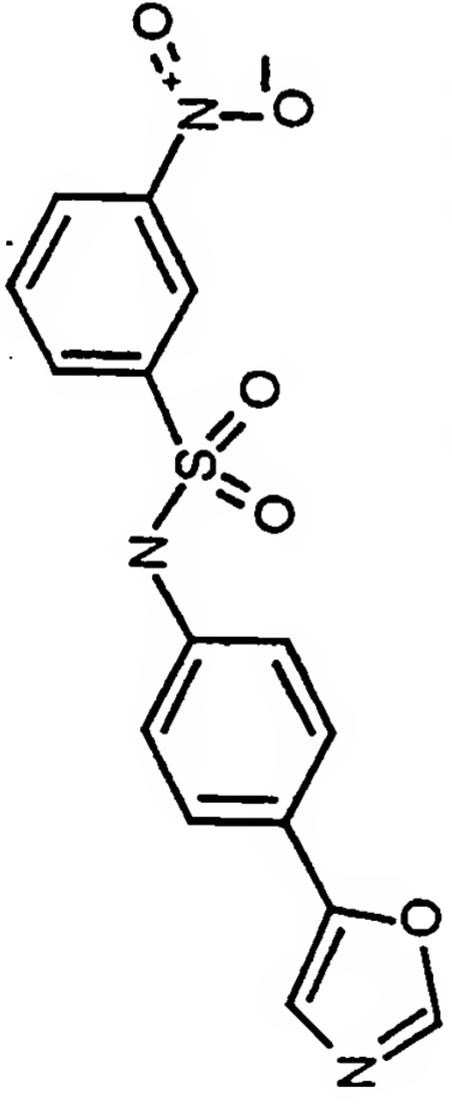
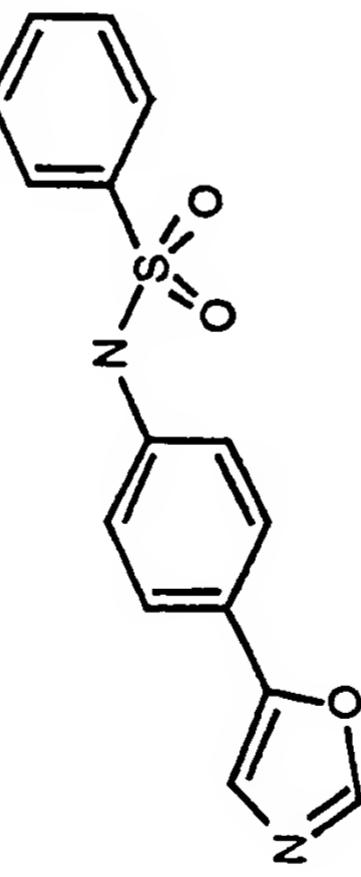
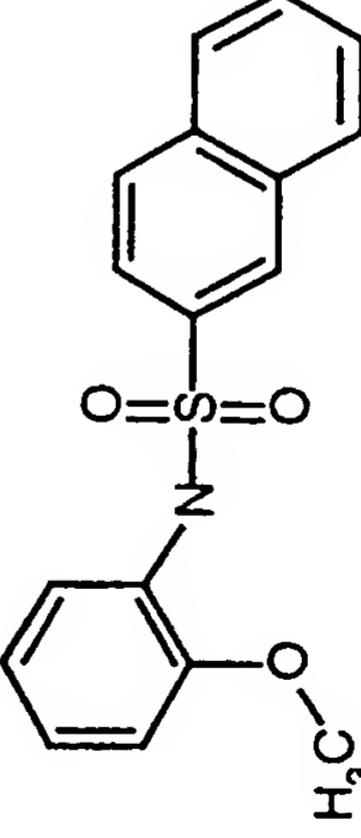
| Molecular Structure | | |
|---------------------|---|---|
| Compd | | |
| 175 |  |  |
| 172 |  |  |
| 173 | |  |
| 174 | | |

| Molecular Structure | | | |
|---------------------|--|---|---|
| Cmpd | | | |
| 181 |  |  |  |
| 178 |  |  |  |

| Molecular Structure | |
|---------------------|---|
| Cmpd | |
| 187 |  |
| 188 |  |
| Molecular Structure | |
| 184 |  |
| 185 |  |
| 186 |  |

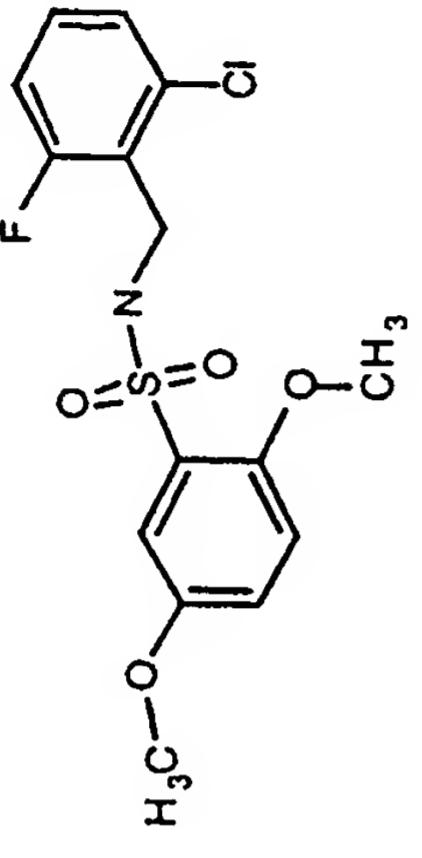
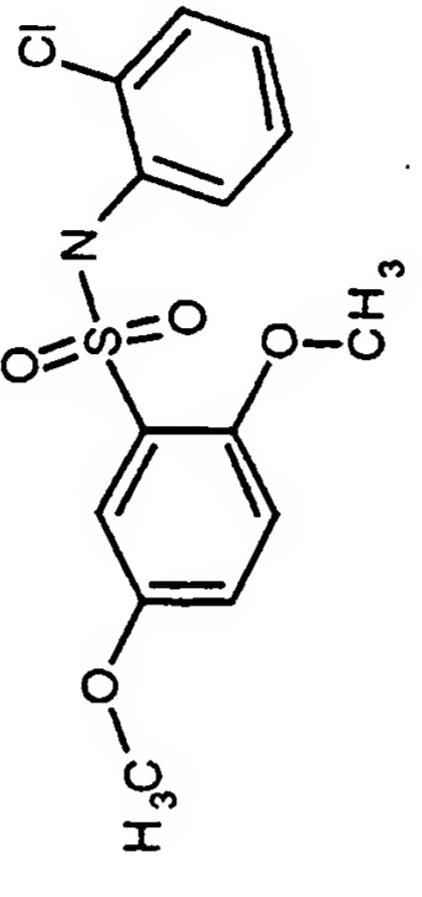
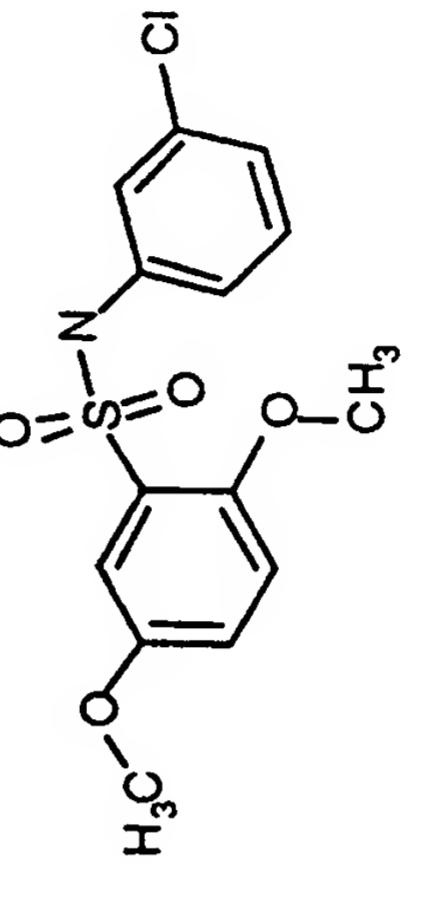
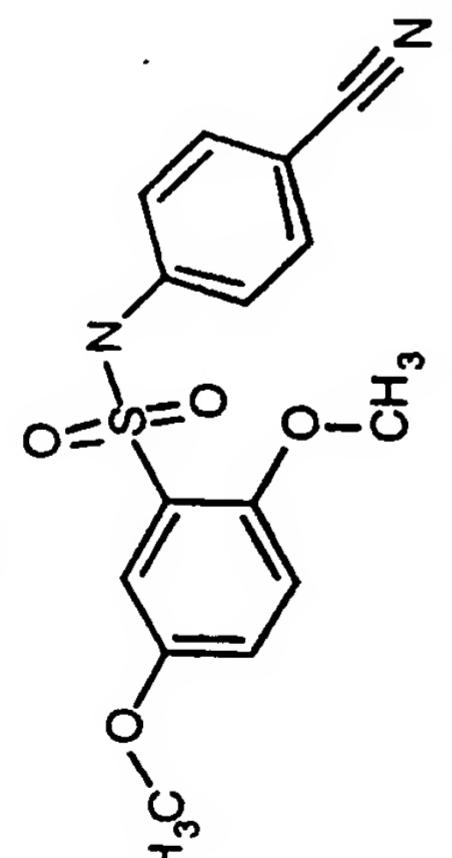
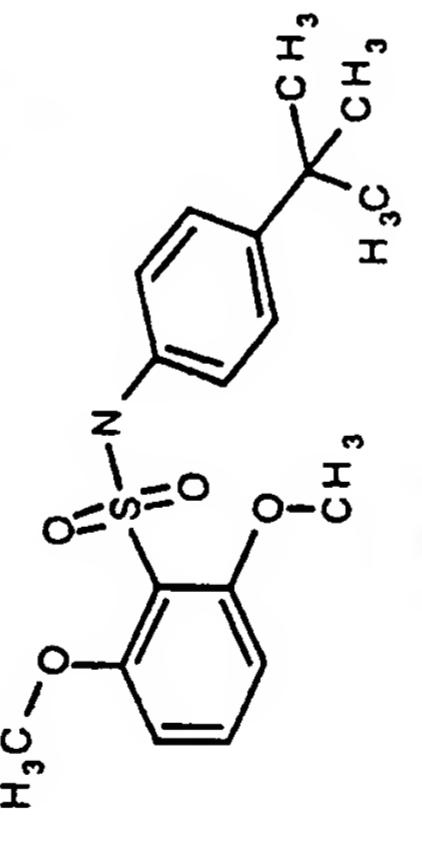
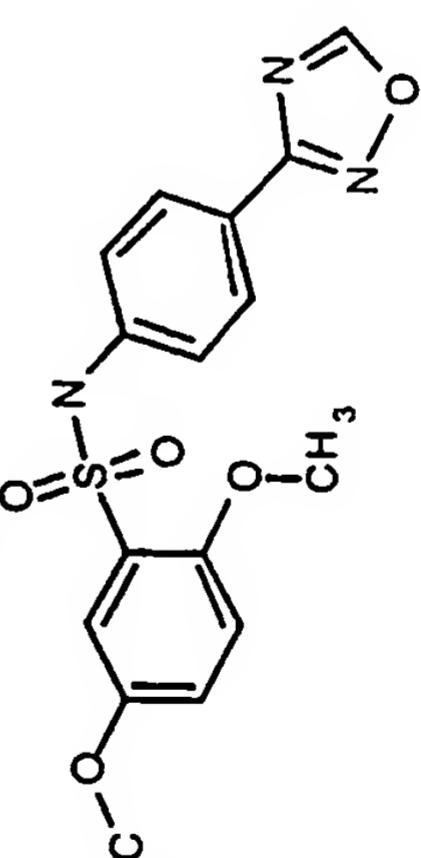
| Cmpd | Molecular Structure | Cmpd | Molecular Structure |
|------|--|------|---|
| 190 |  | 194 |  |
| 191 |  | 195 |  |
| 192 |  | 196 |  |
| 193 |  | 197 |  |

| Cmpd: | Molecular Structure | Cmpd: | Molecular Structure |
|-------|--|-------|---|
| 198 |  | 202 |  |
| 199 |  | 203 |  |
| 200 |  | 204 |  |
| 201 |  | | |

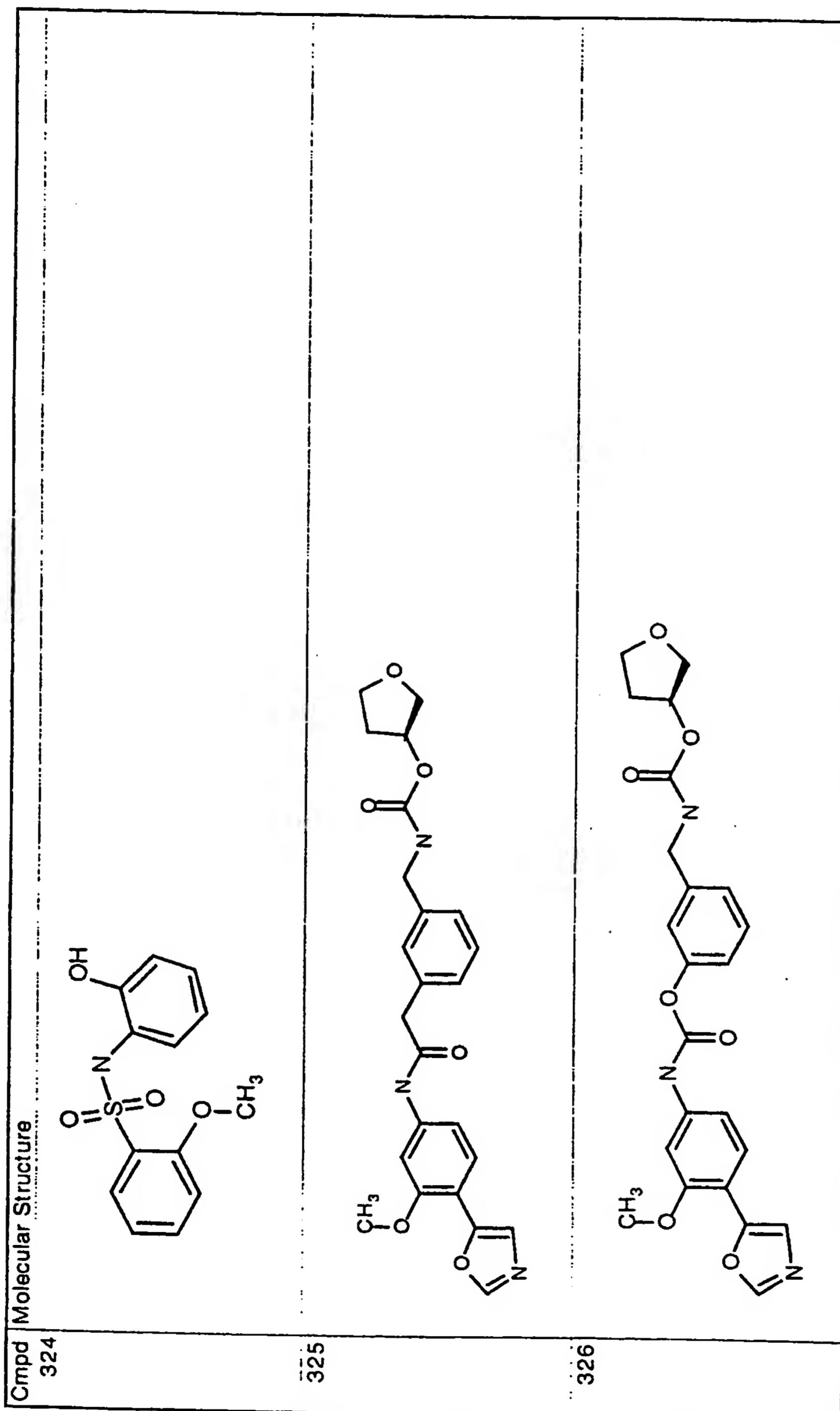
| Cmpd | Molecular Structure |
|------|---|
| 304 |  |
| 305 |  |
| 306 |  |
| 300 |  |
| 301 |  |
| 302 |  |

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| Cmpd | Molecular Structure | Cmpd | Molecular Structure | Cmpd | Molecular Structure |
|------|---------------------|------|---------------------|------|---------------------|
| 307 | | 312 | | 313 | |
| 303 | | 308 | | 309 | |

| Cmpd | Molecular Structure |
|------|---|
| 314 |  |
| 315 |  |
| 320 |  |
| 310 |  |
| 311 |  |
| 316 |  |

| Cmpd | Molecular Structure |
|------|---------------------|
| 321 | |
| 322 | |
| 323 | |
| Cmpd | Molecular Structure |
| 317 | |
| 318 | |
| 319 | |



The compounds of this invention may contain one or more asymmetric carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers.

- 5 All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration.

Combinations of substituents and variables envisioned by this invention are only those that result 10 in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed 15 herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a 20 week.

As used herein, the compounds of this invention, are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means 25 any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and 30 prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally

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administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

- 5 Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of the compounds of this invention.

Pharmaceutically acceptable salts of the
10 compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate,
15 camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,
20 methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as
25 sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

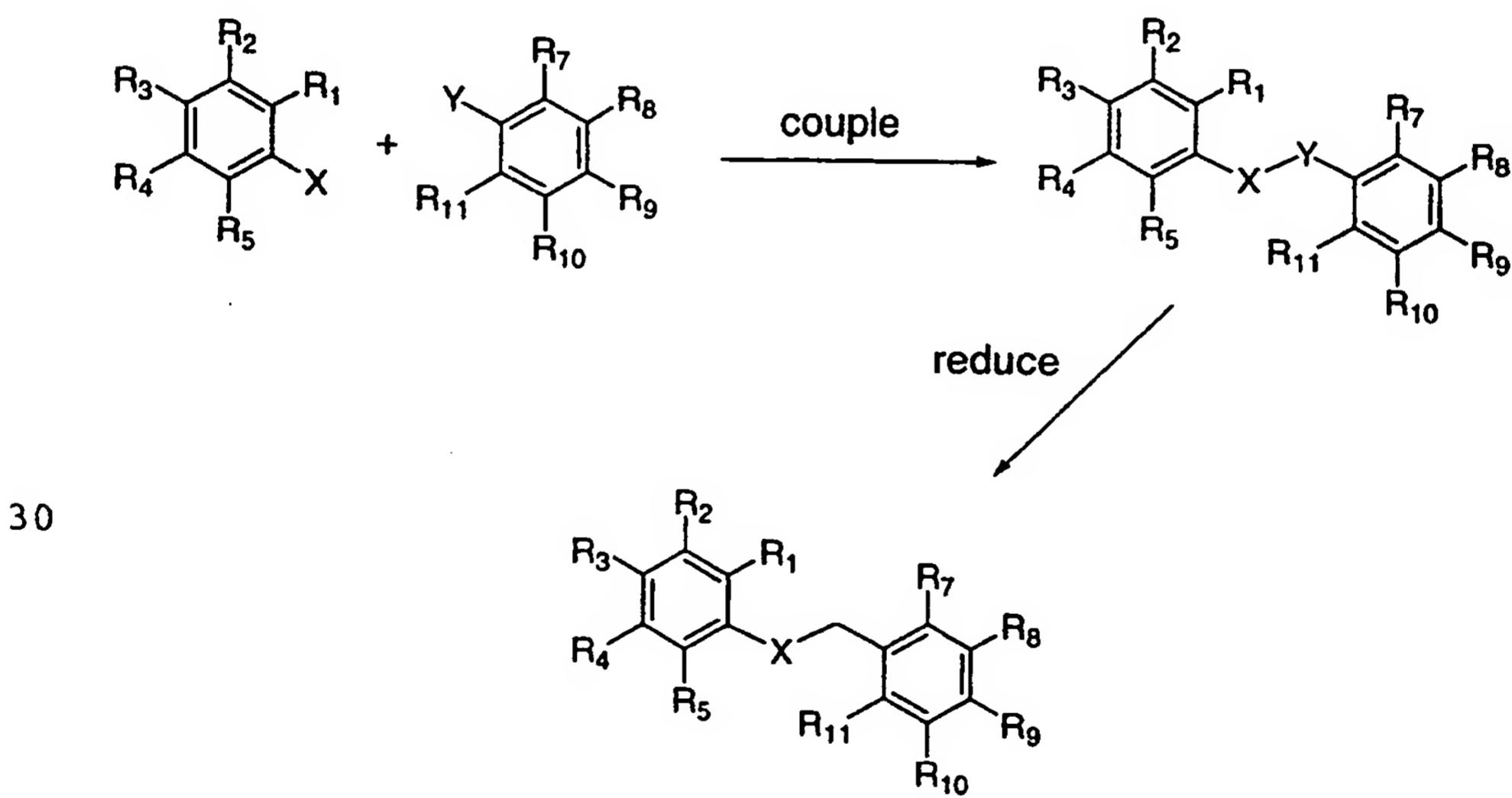
30 Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride,

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bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently 10 synthesized from readily available starting materials.

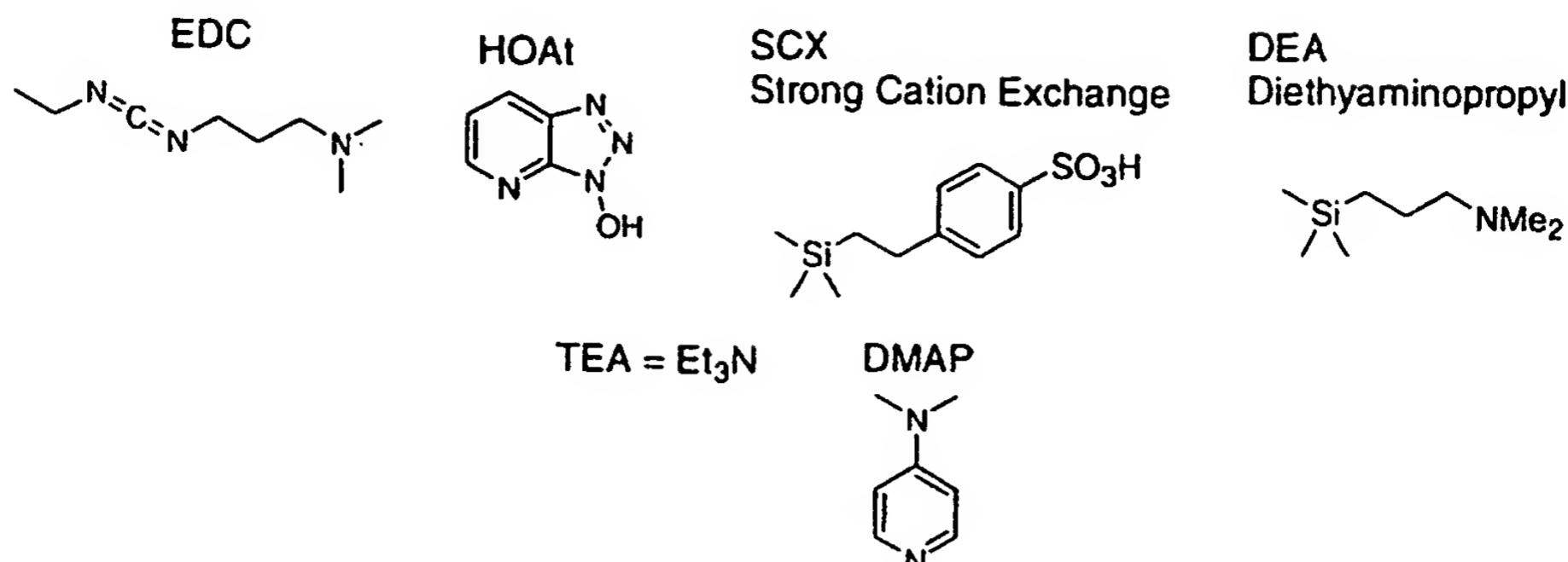
In general, compounds of this invention are conveniently obtained via methods illustrated in Scheme 1 below:



The coupling step indicated in Scheme 1 was 40 used to produce the benzamide, arylacetamide, sulfonamide, carbamate and thiocarbamate compounds of this invention.

Materials used for coupling and reduction are indicated below:

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For benzamide synthesis, A in the initial step was $-\text{N}(\text{H})\text{R}_6$ and B was $-\text{C}(\text{O})\text{OH}$ or $-\text{C}(\text{O})\text{Cl}$. The coupling was performed in the presence of EDC, HOAt and CH_3CN .

For arylacetamide synthesis, A in the initial 5 step was $-\text{N}(\text{H})\text{R}_6$ and B was $-\text{Y}-\text{C}(\text{O})\text{OH}$ or $-\text{Y}-\text{C}(\text{O})\text{Cl}$. The coupling was performed in the presence of EDC, CH_2Cl_2 , and DMAP.

For sulfonamide synthesis, A in the initial step was $\text{N}(\text{H})\text{R}_6$ and B was $\text{S}(\text{O})_2\text{Cl}$. The coupling was 10 performed in the presence of TEA and CH_2Cl_2 .

For carbamate synthesis, A in the initial step was $\text{N}(\text{H})\text{R}_6$ and B was $\text{OC}(\text{O})\text{Cl}$. The coupling was performed in the presence of TEA and CH_2Cl_2 .

For thiocarbamate synthesis, A in the initial 15 step was $\text{NC}(\text{O})$ and B was SH . The coupling was performed in the presence of DMAP and CH_2Cl_2 .

The reduction step indicated in scheme 1 was used to produce the benzyl amines of this invention. In the coupled molecule $\text{A}'-\text{B}'$ was $\text{N}(\text{R}_6)-\text{C}(\text{O})$ and reduction 20 was carried out in the presence of $\text{BH}_3 \cdot \text{THF}/\text{THF}$.

The above reactions were carried out at room temperature for 5 hours with constant shaking.

Once synthesized, compounds were purified by solid phase extraction (SPE) on a bed of Varian DEA and

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Varian SCX sorbents in a 2:1 ratio (w/w): 180 mg was packed into 1 mL cartridges.

The procedure is as follows:

| Event | Volume | Flow rate |
|-------------------|--------|-----------|
| condition sorbent | 1.5 ml | 3 mL/min |
| load and collect | 0.9 ml | 3 mL/min |
| elute | 1.5 ml | 1 mL/min |

- 5 The collected solution contained product at >95% purity (HPLC: 210 nm) with traces of O-acylated impurity. Yields were typically 8-12 mg.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise
10 a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an
15 alternate sequence or order to give the desired compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are
20 known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter
25 metabolism and alter rate of excretion.

The novel compounds of the present invention are excellent ligands for IMPDH. Accordingly, these compounds are capable of targeting and inhibiting IMPDH

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enzyme. Inhibition can be measured by various methods, including, for example, IMP dehydrogenase HPLC assays (measuring enzymatic production of XMP and NADH from IMP and NAD) and IMP dehydrogenase spectrophotometric assays 5 (measuring enzymatic production of NADH from NAD). [See C. Montero et al., Clinica Chimica Acta, 238, pp. 169-178 (1995)].

Compositions of this invention comprise a compound of this invention or a salt thereof; an 10 additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound; and any pharmaceutically acceptable carrier, adjuvant or vehicle. Alternate 15 compositions of this invention comprise a compound of this invention or a salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such composition may optionally comprise an additional agent selected from an immunosuppressant, an anti-cancer agent, 20 an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound. Preferably, the compositions of this invention are pharmaceutical compositions.

The term "pharmaceutically acceptable carrier 25 or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic 30 amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical

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compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as α -tocopherol polyethyleneglycol 1000 succinate, 5 surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of 10 saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based 15 substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypolyene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified 20 derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of this invention.

The pharmaceutical compositions of this 25 invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain 30 any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically

acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular,
5 intra-articular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as
10 a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a
15 sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride
20 solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are
25 useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such
30 as those described in Pharmacopeia Helvetica, Ph. Helv., or a similar alcohol, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the

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formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are
5 commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as
10 magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase
15
20 is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of
25 suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to
30 release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application 5 topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited 10 to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound 15 suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The 20 pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

25 The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, 30 employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,

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fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

- Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 5 0.5 and about 75 mg/kg body weight per day of the IMPDH inhibitory compounds described herein are useful in a monotherapy and/or in combination therapy for the prevention and treatment of IMPDH mediated disease. Typically, the pharmaceutical compositions of this 10 invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single 15 dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.
- 20 When the compositions of this invention comprise a combination of an IMPDH inhibitor of this invention and one or more additional therapeutic or prophylactic agents, both the IMPDH inhibitor and the additional agent should be present at dosage levels of 25 between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention.
- 30 Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

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- According to one embodiment, the pharmaceutical compositions of this invention comprise an additional immunosuppression agent. Examples of additional immunosuppression agents include, but are not limited to,
- 5 cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.
- According to an alternate embodiment, the pharmaceutical compositions of this invention may
- 10 additionally comprise an anti-cancer agent. Examples of anti-cancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A,
- 15 phenothiazines, interferon and thioxanthenes.

- According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-viral agent. Examples of anti-viral agents include, but are not limited to,
- 20 Cytovene, Ganciclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, AZT, and acyclovir.

- According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-vascular hyperproliferative agent. Examples of anti-vascular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic acid, ciprostone, trapidil, ACE inhibitors, low molecular weight heparin,
- 25 mycophenolic acid, rapamycin and 5-(3'-pyridinylmethyl)benzofuran-2-carboxylate.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

In an alternate embodiment, this invention provides methods of treating or preventing IMPDH mediated disease in a mammal comprising the step of administrating to said mammal any of the pharmaceutical compositions and combinations described above. If the pharmaceutical composition only comprises the IMPDH inhibitor of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an anti-inflammatory agent, immunosuppressant, an anti-cancer agent, an anti-viral agent, or an anti-vascular hyperproliferation compound. Such additional agent may be administered to the mammal

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prior to, concurrently with, or following the administration of the IMPDH inhibitor composition.

In a preferred embodiment, these methods are useful in suppressing an immune response in a mammal.

- 5 Such methods are useful in treating or preventing diseases, including, transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), graft versus host disease, and autoimmune 10 diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, diabetes, mellitus myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, 15 eye uveitis, Grave's disease, Hashimoto's thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic adrenal insufficiency, polyglandular autoimmune syndrome, glomerulonephritis, scleroderma, lichen planus, viteligo 20 (depigmentation of the skin), autoimmune thyroiditis, and alveolitis.

These methods comprise the step of administering to the mammal a composition comprising a compound of this invention and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional immunosuppressant and a pharmaceutically acceptable adjuvant.

30 Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of this invention; an additional

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immunosuppressive agent and a pharmaceutically acceptable adjuvant.

In an alternate preferred embodiment, these methods are useful for inhibiting viral replication in a mammal. Such methods are useful in treating or preventing DNA and RNA viral diseases caused by infection for example, by orthomyxoviruses (influenza viruses types A and B), paramyxoviruses (respiratory syncytial virus (RSV), subacute sclerosing panencephalitis (SSPE) virus) 10 measles and parainfluenza type 3), herpesviruses (HSV-1, HSV-2, HHV-6, HHV-7, HHV-8, Epstein Barr Virus (EBV), cytomegalovirus (HCMV) and varicella zoster virus (VZV)), retroviruses (HIV-1, HIV-2, HTLV-1, HTLV-2), flavi- and pestiviruses (yellow fever virus (YFV), hepatitis C virus 15 (HCV), dengue fever virus, bovine viral diarrhea virus (BVDV), hepatotropic viruses (hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, hepatitis D virus (HDV), hepatitis E virus (HEV), hepatitis G virus (HGV), Crimean-Congo hemorrhagic fever virus (CCHF), 20 bunyaviruses (Punta Toro virus, Rift Valley fever virus (RVFV), and sandfly fever Sicilian virus), Hantaan virus, Caraparu virus), human papilloma viruses, encephalitis viruses (La Crosse virus), arena viruses (Junin and Tacaribe virus), reovirus, vesicular stomatitis virus, 25 rhinoviruses, enteroviruses (polio virus, coxsackie viruses, encephalomyocarditis virus (EMC)), Lassa fever virus, and togaviruses (Sindbis and Semlike forest viruses) and poxviruses (vaccinia virus), adenoviruses, rubiola, and rubella.

30 These methods comprise the step of administering to the mammal a composition comprising a compound of this invention, and a pharmaceutically

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acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional anti-viral agent and a pharmaceutically acceptable adjuvant.

5

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of this invention; an additional anti-viral agent and a pharmaceutically acceptable adjuvant.

10

In another alternate preferred embodiment, these methods are useful for inhibiting vascular cellular hyperproliferation in a mammal. Such methods are useful in treating or preventing diseases, including, restenosis, stenosis, atherosclerosis and other

15

hyperproliferative vascular disease.

20

These methods comprise the step of administering to the mammal a composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant.

25

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of this invention; an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant.

30

In another alternate preferred embodiment, these methods are useful for inhibiting tumors and cancer in a mammal. Such methods are useful in treating or

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preventing diseases, including, tumors and malignancies, such as lymphoma, leukemia and other forms of cancer.

These methods comprise the step of administering to the mammal a composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional anti-tumor or anti-cancer agent and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of this invention; an additional anti-tumor or anti-cancer agent and a pharmaceutically acceptable adjuvant.

In another alternate preferred embodiment, these methods are useful for inhibiting inflammation and inflammatory diseases in a mammal. Such methods are useful in treating or preventing diseases, including, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma and adult respiratory distress syndrome.

These methods comprise the step of administering to the mammal a composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an anti-inflammatory agent and a pharmaceutically acceptable adjuvant.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are

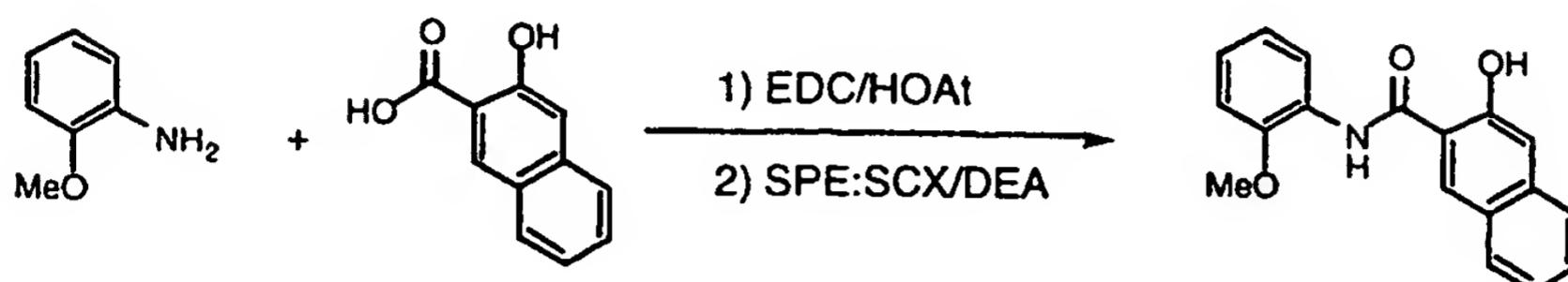
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not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

5

Synthesis of Compound 100



Solutions of acid (80 μ L, 32 μ mol) and aniline (100 μ L, μ mol) in THF were dispensed into a teflon 96-well plate. A solution containing 0.4M EDC.HCl and 0.4M HOAt in MeCN (100 μ L, 40 μ mol) was added and the reactions mixed in a vortex shaker for 5h. MeOH (500 μ L) was added.

10

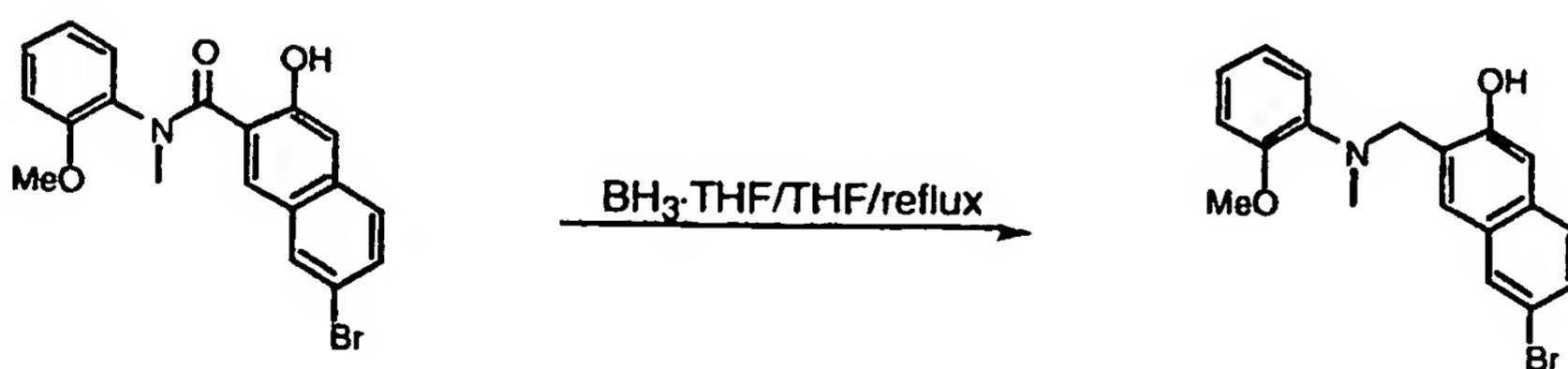
HPLC-MS data: retention time in 0.1% TFA: 8.81 min.

LRMS (EI): 294.1 ($M + H$, relative intensity 100%)

15

EXAMPLE 2

Synthesis of Compound 103:



20

To a room temperature solution of the amide (65 mg, 0.168 mmole) in 5 ml of THF was added $BH_3 \cdot THF$ (0.45 ml, 0.539 mmole). The resulting mixture was heated to reflux overnight, then cooled to room temperature, and 25 concentrated *in vacuo*. The resulting crude product was

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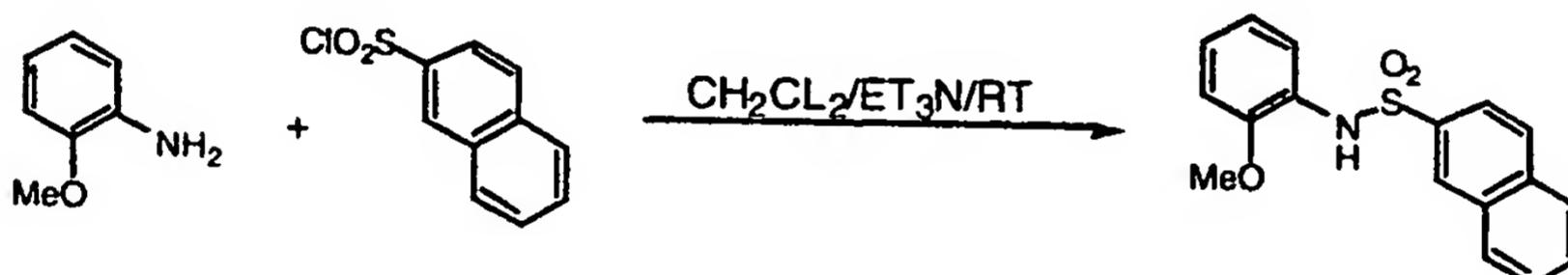
diluted in 5 ml of saturated HCl in MeOH and heated to reflux for 3 hours. The resulting mixture was cooled to room temperature, diluted with ethyl acetate, washed successively with saturated NaHCO₃, water, brine, then 5 dried over Na₂SO₄. The crude product was purified by silica-gel chromatography (9/1 hexanes/ether) to give 33 mg (53% yield) of the desired benzylamine.

¹H NMR (CDCl₃, 500 MHz): 10.51 (1H, broad s); 7.96 (1H, 10 s); 7.67 (1H, d); 7.57 (1H, s); 7.55 (1H, dd); 7.34 (1H, s); 7.32 (1H, d); 7.26 (1H, dd); 7.09 (1H, dd); 7.04 (1H, d); 4.41 (2H, s); 4.06 (3H, s); 2.75 (3H, s).

EXAMPLE 3

15

Synthesis of Compound 302



To a 0°C solution of the sulfonyl chloride (100 mg, 0.44 mmoles) in CH₂Cl₂ (5 mL) was added *o*-anisidine (45mL, 0.44 mmoles). The resulting mixture was allowed 20 to warm to room temperature and stirred overnight. The crude reaction was diluted with ethyl acetate, washed with sat. NaHCO₃, 0.5 N HCl, brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by MPLC to give the 88 mg (64%) of the 25 desired sulfonamide.

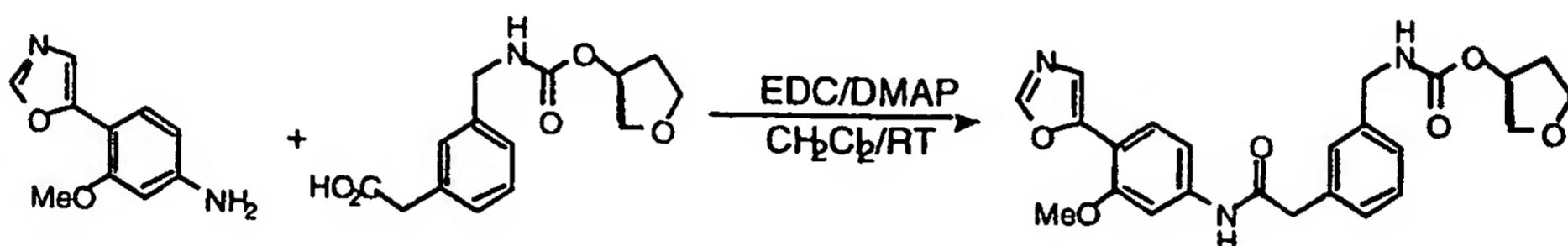
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¹H NMR (CDCl₃, 500 MHz): 8.31 (1H, s); 7.82 (3H, m); 7.70 (1H, d); 7.54 (3H, m); 7.06 (1H, s); 6.97 (1H, dd); 6.88 (1H, dd); 6.67 (1H, d); 3.56 (3H, s)

5

EXAMPLE 4

Synthesis of Compound 325



To a room temperature solution of the acid (76
 10 mg, 0.272 mmole) in CH₂Cl₂ (4 ml) was added the aniline
 (57 mg, 0.30 mmole), EDC (104 mg, 0.544 mmole) and DMAP
 (catalytic amount). The resulting mixture was stirred at
 room temperature for 16 hours, then diluted with ethyl
 acetate and water. The phases were separated and the
 15 organic phase was washed with 1.0 N HCl, sat. NaHCO₃,
 brine, dried over Na₂SO₄, filtered and concentrated *in*
vacuo. Crude product was purified via flash
 chromatography to give 56 mg (46%) of the desired amide
 as a white solid.

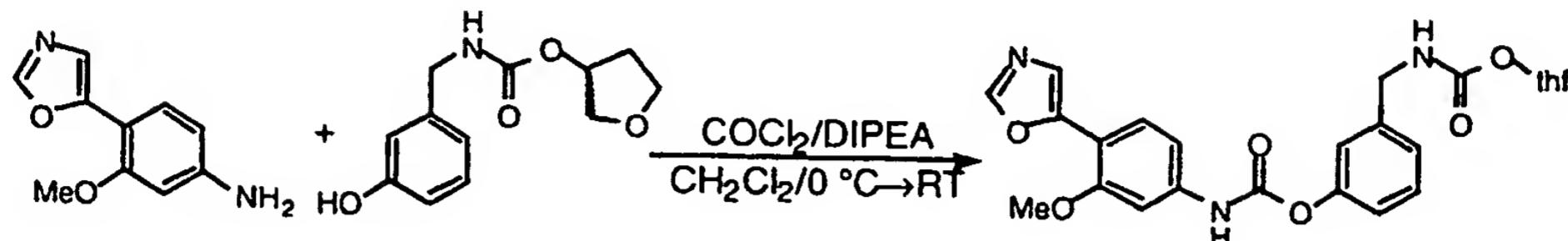
20

¹H NMR (DMSO-d₆, 500 MHz): 10.50 (1H, s); 8.40 (1H, s);
 7.85 (1H, broad t); 7.65 (1H, d); 7.45 (1H, s); 7.50-7.35
 (3H, m); 7.30-7.10 (4H, m); 5.15 (1H, broad m); 4.20 (2H,
 d); 3.90 (3H, s); 3.80-3.60 (4H, m); 2.10 (1H, m); 1.85
 25 (1H, m).

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EXAMPLE 5

Synthesis of Compound 326



5 To a stirred, 0°C solution of the phenol (86 mg, 0.362 mmole) in CH_2Cl_2 (1.5 mL) was added DIPEA (59 mL, 0.434 mmole) and phosgene (742 mL, 0.74 mmole, 1.0 M in PhMe). The resulting solution was warmed to room temperature, stirred for 2.5 hours, then concentrated *in vacuo*.
 10 The resulting chloroformate was diluted in CH_2Cl_2 (2 mL), cooled to 0 °C, then treated with a CH_2Cl_2 solution of the aniline (83 mg, 0.434 mmole) and DIPEA (74 mL, 0.543 mmole). The resulting mixture was stirred
 15 at room temperature overnight, then diluted in ethyl acetate and water. The phases were separated, the organic phase washed with sat. NaHCO_3 , brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to give 40 mg (24%) of the desired carbamate as a slightly yellow
 20 foam.

^1H NMR (DMSO-d_6 , 500 MHz): 10.40 (1H, s); 8.38 (1H, s);
 7.80 (1H, broad t); 7.62 (1H, d); 7.58 (1H, d); 7.45 (1H, s);
 7.30-7.10 (5H, m); 5.12 (1H, m); 4.18 (2H, d); 3.90 (3H, s);
 25 3.80-3.60 (4H, m); 3.65 (2H, s); 2.10 (1H, m);
 1.95 (1H, m).

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EXAMPLE 6

IMPDH Activity Inhibition Assay

IMP dehydrogenase activity was assayed 5 following an adaptation of the method first reported by Magasanik. [B. Magasanik et al., J. Biol. Chem., 226, p. 339 (1957), the disclosure of which is herein incorporated by reference]. Enzyme activity was measured spectrophotometrically, by monitoring the increase in 10 absorbance at 340 nm due to the formation of NADH (ϵ_{340} is $6220\text{ M}^{-1}\text{ cm}^{-1}$). The reaction mixture contained 0.1 M Tris pH 8.0, 0.1 M KCl, 3 mM EDTA, 2 mM DTT, 0.1 M IMP and enzyme (IMPDH human type II) at a concentration of 15 to 50 nM. This solution is incubated at 37°C for 10 15 minutes. The reaction is started by adding NAD to a final concentration of 0.1M and the initial rate is measured by following the linear increase in absorbance at 340 nm for 10 minutes. For reading in a standard spectrophotometer (path length 1 cm) the final volume in 20 the cuvette is 1.0 ml. The assay has also been adapted to a 96 well microtiter plate format; in this case the concentrations of all the reagents remain the same and the final volume is decreased to 200 μl .

For the analysis of inhibitors, the compound in 25 question is dissolved in DMSO to a final concentration of 20 mM and added to the initial assay mixture for preincubation with the enzyme at a final volume of 2- 5% (v/v). The reaction is started by the addition of NAD, and the initial rates measured as above. K_i 30 determinations are made by measuring the initial velocities in the presence of varying amounts of inhibitor and fitting the data using the tight-binding

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equations of Henderson (Henderson, P. J. F. (1972) Biochem. J. 127, 321].

These results are shown in Table 2. Category "A" indicates a K_I of less than 10 μM , category "B" 5 indicates a K_I of between 10 and 20 μM , category "C" indicates a K_I greater than 20 μM .

Table 2. IMPDH inhibitory activity.

| Compound | <i>Ki</i> | Compound | <i>Ki</i> | Compound | <i>Ki</i> |
|-----------------|------------------|-----------------|------------------|-----------------|------------------|
| 100 | A | 143 | A | 188 | B |
| 101 | B | 144 | B | 190 | C |
| 102 | A | 145 | B | 191 | C |
| 103 | B | 146 | B | 192 | C |
| 104 | B | 147 | A | 193 | B |
| 105 | B | 148 | B | 194 | C |
| 106 | B | 149 | B | 195 | B |
| 107 | B | 150 | B | 196 | B |
| 108 | B | 151 | A | 197 | C |
| 109 | A | 152 | B | 198 | C |
| 110 | B | 153 | A | 199 | C |
| 111 | A | 154 | B | 200 | B |
| 112 | B | 155 | B | 201 | B |
| 113 | A | 156 | B | 202 | C |
| 114 | A | 157 | B | 203 | C |
| 115 | A | 159 | B | 204 | C |
| 116 | C | 160 | B | 300 | B |
| 117 | C | 161 | A | 301 | B |
| 118 | B | 162 | B | 302 | B |
| 119 | C | 163 | B | 303 | C |
| 120 | B | 164 | A | 304 | C |
| 121 | B | 165 | B | 305 | A |
| 122 | B | 166 | B | 306 | B |
| 123 | A | 167 | B | 307 | B |
| 124 | A | 168 | B | 308 | B |
| 125 | B | 169 | A | 309 | B |
| 126 | A | 170 | A | 310 | B |
| 127 | A | 171 | B | 311 | B |
| 128 | B | 172 | A | 312 | B |
| 129 | B | 173 | B | 313 | B |
| 130 | B | 174 | B | 314 | B |
| 131 | B | 175 | A | 315 | B |
| 132 | B | 177 | B | 316 | B |

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| Compound | Ki | Compound | Ki | Compound | Ki |
|-----------------|-----------|-----------------|-----------|-----------------|-----------|
| 133 | B | 178 | A | 317 | B |
| 134 | B | 179 | B | 318 | B |
| 135 | B | 180 | B | 319 | B |
| 136 | B | 181 | A | 320 | B |
| 137 | B | 182 | A | 321 | B |
| 138 | A | 183 | A | 322 | B |
| 139 | A | 184 | B | 323 | B |
| 140 | A | 185 | A | 324 | B |
| 141 | A | 186 | B | 325 | A |
| 142 | B | 187 | B | 326 | A |

Other compounds of this invention will also have IMPDH inhibitory activity.

5

EXAMPLE 7

Anti-Viral Assays

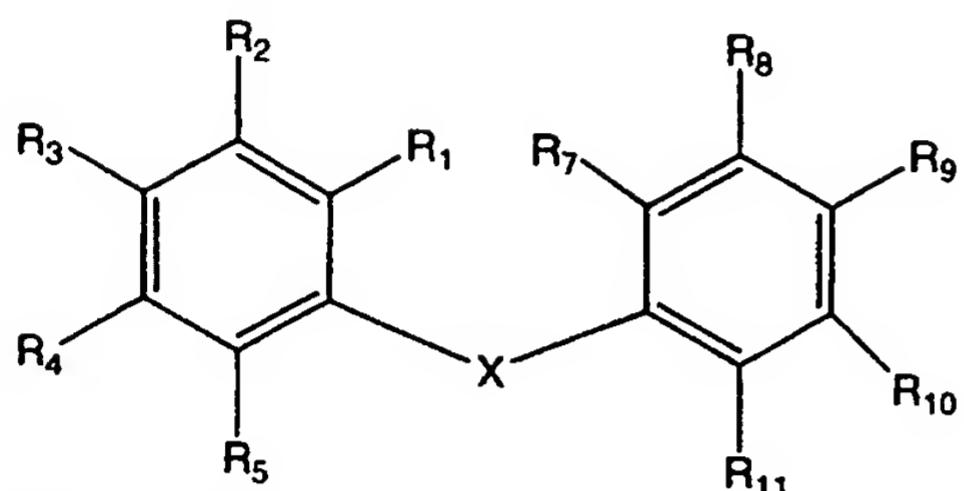
The anti-viral efficacy of compounds may be evaluated in various in vitro and in vivo assays. For 10 example, compounds may be tested in in vitro viral replication assays. In vitro assays may employ whole cells or isolated cellular components. In vivo assays include animal models for viral diseases. Examples of such animal models include, but are not limited to, 15 rodent models for HBV or HCV infection, the Woodchuck model for HBV infection, and chimpanzee model for HCV infection.

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that my 20 basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been 25 presented hereinbefore by way of example.

CLAIMS

We claim:

1. A compound of the formula:



wherein:

X is selected from $-C(O)-N(R_6)-$, $-N(R_6)-C(O)-$,
 $-CH_2-N(R_6)-$, $-N(R_6)-CH_2-$, $-N(R_6)-S(O)_2-$, $-S(O)_2-N(R_6)-$,
 $-C(R_{12})(R_{12})-C(O)-$, $-C(O)-C(R_{12})(R_{12})-$, $-C(R_{12})(R_{12})-S(O)_2-$,
 $-S(O)_2-C(R_{12})(R_{12})-$, $-S(O)_2-O-$, $-O-S(O)_2-$, $-NR_6-C(O)-Y-$ or
 $Y-C(O)-NR_6-$; wherein

each R_6 is independently selected from hydrogen,
 C_1-C_4 straight or branched alkyl, C_2-C_4 straight or
branched alkenyl or alkynyl, Ar-substituted- C_1-C_4
straight or branched alkyl, or Ar-substituted- C_2-C_4
straight or branched alkenyl or alkynyl; wherein

R_6 is optionally substituted with up to 3
substituents independently selected from halo,
hydroxy, nitro, cyano or amino;

each R_{12} is independently selected from R_6 , W-
 $[C_1-C_4$ straight or branched alkyl], W- $[C_2-C_4$ straight
or branched alkenyl or alkynyl], Ar-substituted-[W-
 $[C_1-C_4$ straight or branched alkyl]], Ar-substituted-
[W- $[C_2-C_4$ straight or branched alkenyl or alkynyl]],
O-Ar, $N(R_6)-Ar$, S-Ar, $S(O)-Ar$, $S(O)_2-Ar$, $S-C(O)H$,
 $N(R_6)-C(O)H$, or O-C(O)H; wherein

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W is O-, O-C(O)-, S-, S(O)-, S(O)₂-, S-C(O)-,
N(R₆)-, or N(R₆)-C(O)-; and wherein

each R₁₂ is optionally and independently substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

Y is selected from -O-, -S-, -C≡C-, -C(R₁₂)₂-
C(R₁₂)₂-, -C(R₁₂)₂- or -C(R₁₂)=C(R₁₂)-;

each of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₁ is independently selected from hydrogen, halo, hydroxy, cyano, nitro, amino, -C(O)NH₂, Z-[(C₁-C₄)-straight or branched alkyl], Z-[(C₂-C₄)-straight or branched alkenyl or alkynyl], Ar-substituted-[(C₁-C₄)-straight or branched alkyl], Ar-substituted-[(C₂-C₄)-straight or branched alkenyl or alkynyl], Ar, Q-Ar, [(C₁-C₄)-straight or branched alkyl]-Q-Ar, [(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, O-[(C₁-C₄)-straight or branched alkyl]-Q-Ar, O-[(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, [C₁-C₄ straight or branched alkyl]-Q-R₁₃, [C₂-C₄ straight or branched alkenyl or alkynyl]-Q-R₁₃, or any two adjacent R groups may be taken together with the carbon atoms to which they are bound to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring; wherein

Z is selected from a bond, O-, S-, S(O)₂-, C(O)-, OC(O)-, or N(H)C(O)-;

Q is selected from O, -O-C(O)-, -C(O)-O-, -N(H)-C(O)-O-, -O-N(H)-C(O)-, -N(H)-C(O)-, -C(O)-N(H)-, -O-C(O)-N(H)-, or -C(O)-N(H)-O-;

Ar is selected from phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,

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pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl or phenoxazinyl or other chemically feasible monocyclic, bicyclic or tricyclic ring systems, wherein each ring consists of 5 to 7 ring atoms and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O and S;

R₁₃ is selected from [C₁-C₁₂ straight or branched alkyl] or, [C₂-C₁₂ straight or branched alkenyl or alkynyl]; wherein R₁₃ is optionally substituted with 1 to 4 substituents independently selected from R₁₄ or R₁₅, wherein

each R₁₄ is a monocyclic or a bicyclic ring system consisting of 3 to 7 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, or S; wherein a CH₂ adjacent to said N, O or S maybe substituted with C(O); and wherein R₁₄ optionally comprises up to 2 substituents independently selected from (C₁-C₄)-straight or branched alkyl, (C₂-C₄) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, (CH₂)_n-R₁₆, -S-(CH₂)_n-R₁₆, -S(O)-(CH₂)_n-R₁₆, -S(O)₂-(CH₂)_n-R₁₆, -O-(CH₂)_n-R₁₆, or -N(R₁₈)-(CH₂)_n-R₁₆ wherein n is 0, 1 or 2;

R₁₆ is selected from halogen, -CN, -NO₂, -CF₃, -OCF₃,

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-OH, -S-(C₁-C₄)-alkyl, -S(O)-(C₁-C₄)-alkyl, -S(O)₂-(C₁-C₄)-alkyl, -NH₂, -NH-(C₁-C₄)-alkyl, N((C₁-C₄)-alkyl)₂, COOH, C(O)-O-(C₁-C₄)-alkyl or O-(C₁-C₄)-alkyl; and

each R₁₅ is independently selected from -OR₁₇, or -N(R₁₈)₂;

R₁₇ is selected from hydrogen, -(C₁-C₆)-straight alkyl, -(C₁-C₆)-straight alkyl-Ar, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, or -(C₁-C₆)-straight alkyl-CN; and

each R₁₈ is independently selected from -(C₁-C₆)-straight or branched alkyl, -(C₁-C₆)-straight or branched alkyl-Ar, -(C₁-C₆)-straight alkyl-CN, -(C₁-C₆)-straight alkyl-OH, -(C₁-C₆)-straight alkyl-OR₁₇, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, -S(O)₂-(C₁-C₆)-straight or branched alkyl, or -S(O)₂-Ar; wherein

any alkyl, alkenyl or alkynyl group is optionally substituted with 1 to 3 independently selected halo groups; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally substituted with 1 to 3 substituents independently selected from halo, hydroxy, nitro, cyano, amino, (C₁-C₄)-straight or branched alkyl; O-(C₁-C₄)-straight or branched alkyl, (C₂-C₄)-straight or branched alkenyl or alkynyl, or O-(C₂-C₄)-straight or branched alkenyl or alkynyl;

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally benzofused; with the provisos that:

at least two of R₁, R₂, R₃, R₄, or R₅ is hydrogen;

no more than two of R₁, R₂, R₃, R₄, or R₅ comprises Ar;

at least two of R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen; and

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no more than two of R₇, R₈, R₉, R₁₀ or R₁₁ comprises Ar;

when X is -NH-S(O)₂- or -S(O)₂-N(H)-,

one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is O-(C₁-C₄)-straight or branched alkyl, and

seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, then

the remaining two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are not bound together to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring;

when X is -NH-S(O)₂- or -S(O)₂-N(H)-,

two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are O-(C₁-C₄)-straight or branched alkyl, and

seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, then

the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is not -NO₂, -CN or -Ar;

when X is -NH-S(O)₂- or -S(O)₂-N(H)-,

two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are O-(C₁-C₄)-straight or branched alkyl, and

six of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, then

the remaining two of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are not both halo;

when X is -NH-S(O)₂- or -S(O)₂-N(H)-, and

one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is Ar, then

the remaining 9 of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are not each hydrogen;

when X is -N(H)-C(O)-S- or -S-C(O)-N(H)-,

one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is -OH, and

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eight of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, then

the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is not halo;

when wherein X is -N(H)-C(O)-S- or -S-C(O)-N(H)-,
one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is -OH,
seven of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ are hydrogen, and

one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is O-(C₁-C₄)-straight or branched alkyl, then

the remaining one of R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ or R₁₁ is not halo or (C₁-C₄)-straight or branched alkyl.

2. The compound according to claim 1, wherein X is selected from -C(O)-N(R₆)-, -N(R₆)-C(O)-, -CH₂-N(R₆)-, or -N(R₆)-CH₂-.

3. The compound according to claim 1, wherein R₁ is selected from H, (C₁-C₄)-straight or branched alkyl, OH, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano or S-(C₁-C₄)-straight or branched alkyl.

4. The compound according to claim 2, wherein R₁ is H and R₂ is not H.

5. The compound according to claim 1, wherein R₂ is selected from H, (C₁-C₄)-straight or branched alkyl, Ar, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano, C(O)NH₂ or S(O)₂-(C₁-C₄)-straight or branched alkyl.

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6. The compound according to claim 5, wherein R₂ is H.

7. The compound according to claim 1, wherein R₃ is selected from H, Ar, cyano, O-(C₁-C₄)-straight or branched alkyl, O-Ar, S-(C₁-C₄)-straight or branched alkyl, CF₃ or OCF₃.

8. The compound according to claim 1, wherein R₄ is selected from H, (C₁-C₄)-straight or branched alkyl, OH, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano or S-(C₁-C₄)-straight or branched alkyl.

9. The compound according to claim 1, wherein R₅ is selected from H, (C₁-C₄)-straight or branched alkyl, Ar, O-(C₁-C₄)-straight or branched alkyl, O-Ar, OCF₃, halo, cyano, C(O)NH₂ or S(O)₂-(C₁-C₄)-straight or branched alkyl.

10. The compound according to claim 9, wherein R₅ is H.

11. The compound according to claim 1, wherein R₇ is selected from H, OH, OC(O)-(C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, O-Ar, amino, or N(H)C(O)-(C₁-C₄)-straight or branched alkyl.

12. The compound according to claim 11, wherein R₇ is OH.

13. The compound according to claim 1, wherein R₆ is H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-

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straight or branched alkyl, or (C₁-C₄)-straight or branched alkyl-N(H)C(O)O-Ar.

14. The compound according to claim 1, wherein R₉ is selected from H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, or R₉ is taken together with R₁₀ and the carbon atoms to which they are bound to form a fused benzene ring.

15. The compound according to claim 14, wherein R₉ and R₁₀ are taken together with the carbon atoms to which they are bound to form a fused benzene ring.

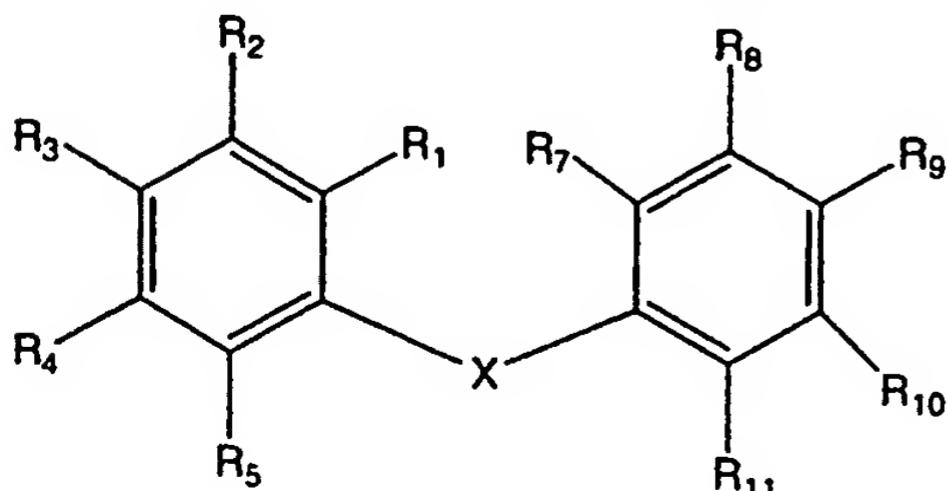
16. The compound according to claim 1, wherein R₁₀ is selected from H, (C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl.

17. The compound according to claim 1, wherein R₁₁ is selected from H, OH, OC(O)-(C₁-C₄)-straight or branched alkyl, O-(C₁-C₄)-straight or branched alkyl, O-Ar, amino, or N(H)C(O)-(C₁-C₄)-straight or branched alkyl.

18. The compound according to claim 17, wherein R₁₁ is H.

19. A composition comprising:

a) a compound of the formula:



wherein:

X is selected from $-C(O)-N(R_6)-$, $-N(R_6)-C(O)-$,
 $-CH_2-N(R_6)-$, $-N(R_6)-CH_2-$, $-N(R_6)-S(O)_2-$, $-S(O)_2-N(R_6)-$,
 $-C(R_{12})(R_{12})-C(O)-$, $-C(O)-C(R_{12})(R_{12})-$, $-C(R_{12})(R_{12})-S(O)_2-$,
 $-S(O)_2-C(R_{12})(R_{12})-$, $-S(O)_2-O-$, $-O-S(O)_2-$, $-NR_6-C(O)-Y-$ or
 $Y-C(O)-NR_6-$; wherein

each R_6 is independently selected from hydrogen,
 C_1-C_4 straight or branched alkyl, C_2-C_4 straight or
branched alkenyl or alkynyl, Ar-substituted- C_1-C_4
straight or branched alkyl, or Ar-substituted- C_2-C_4
straight or branched alkenyl or alkynyl; wherein

R_6 is optionally substituted with up to 3
substituents independently selected from halo,
hydroxy, nitro, cyano or amino;

each R_{12} is independently selected from R_6 , W-
[C_1-C_4 straight or branched alkyl], W-[C_2-C_4 straight
or branched alkenyl or alkynyl], Ar-substituted-[W-
[C_1-C_4 straight or branched alkyl]], Ar-substituted-
[W-[C_2-C_4 straight or branched alkenyl or alkynyl]],
 $O-Ar$, $N(R_6)-Ar$, $S-Ar$, $S(O)-Ar$, $S(O)_2-Ar$, $S-C(O)H$,
 $N(R_6)-C(O)H$, or $O-C(O)H$; wherein

W is $O-$, $O-C(O)-$, $S-$, $S(O)-$, $S(O)_2-$, $S-C(O)-$,
 $N(R_6)-$, or $N(R_6)-C(O)-$; and wherein

each R_{12} is optionally and independently
substituted with up to 3 substituents independently
selected from halo, hydroxy, nitro, cyano or amino;

Y is selected from $-O-$, $-S-$, $-C\equiv C-$, $-C(R_{12})_2-$,
 $C(R_{12})_2-$, $-C(R_{12})_2-$ or $-C(R_{12})=C(R_{12})-$;

each of R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} and R_{11} is
independently selected from hydrogen, halo, hydroxy,
cyano, nitro, amino, $-C(O)NH_2$, Z-[(C_1-C_4)-straight or

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branched alkyl], Z-[(C₂-C₄)-straight or branched alkenyl or alkynyl], Ar-substituted-[(C₁-C₄)-straight or branched alkyl], Ar-substituted-[(C₂-C₄)-straight or branched alkenyl or alkynyl], Ar, Q-Ar, [(C₁-C₄)-straight or branched alkyl]-Q-Ar, [(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, O-[(C₁-C₄)-straight or branched alkyl]-Q-Ar, O-[(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, [C₁-C₄ straight or branched alkyl]-Q-R₁₃, [C₂-C₄ straight or branched alkenyl or alkynyl]-Q-R₁₃, or any two adjacent R groups may be taken together with the carbon atoms to which they are bound to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring; wherein

Z is selected from a bond, O-, S-, S(O)₂-, C(O)-, OC(O)-, or N(H)C(O)-;

Q is selected from O, -O-C(O)-, -C(O)-O-, -N(H)-C(O)-O-, -O-N(H)-C(O)-, -N(H)-C(O)-, -C(O)-N(H)-, -O-C(O)-N(H)-, or -C(O)-N(H)-O-;

Ar is selected from phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl,

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phenazinyl, phenothiazinyl or phenoazinyl or other chemically feasible monocyclic, bicyclic or tricyclic ring systems, wherein each ring consists of 5 to 7 ring atoms and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O and S;

R_{13} is selected from [C_1-C_{12} straight or branched alkyl] or, [C_2-C_{12} straight or branched alkenyl or alkynyl]; wherein R_{13} is optionally substituted with 1 to 4 substituents independently selected from R_{14} or R_{15} , wherein

each R_{14} is a monocyclic or a bicyclic ring system consisting of 3 to 7 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, or S; wherein a CH_2 adjacent to said N, O or S maybe substituted with $C(O)$; and wherein R_{14} optionally comprises up to 2 substituents independently selected from (C_1-C_4)-straight or branched alkyl, (C_2-C_4) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, $(CH_2)_n-R_{16}$, $-S-(CH_2)_n-R_{16}$, $-S(O)-(CH_2)_n-R_{16}$, $-S(O)_2-(CH_2)_n-R_{16}$, $-O-(CH_2)_n-R_{16}$, or $-N(R_{18})-(CH_2)_n-R_{16}$

wherein n is 0, 1 or 2;

R_{16} is selected from halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-OH$, $-S-(C_1-C_4)-alkyl$, $-S(O)-(C_1-C_4)-alkyl$, $-S(O)_2-(C_1-C_4)-alkyl$, $-NH_2$, $-NH-(C_1-C_4)-alkyl$, $N((C_1-C_4)-alkyl)_2$, COOH, $C(O)-O-(C_1-C_4)-alkyl$ or $O-(C_1-C_4)-alkyl$; and

each R_{15} is independently selected from $-OR_{17}$, or $-N(R_{18})_2$;

R_{17} is selected from hydrogen, $-(C_1-C_6)$ -straight alkyl, $-(C_1-C_6)$ -straight alkyl-Ar, $-C(O)-(C_1-C_6)$ -straight or branched alkyl, $-C(O)-Ar$, or $-(C_1-C_6)$ -straight alkyl-CN; and

each R_{18} is independently selected from $-(C_1-C_6)-$

straight or branched alkyl, -(C₁-C₆)-straight or branched alkyl-Ar, -(C₁-C₆)-straight alkyl-CN, -(C₁-C₆)-straight alkyl-OH, -(C₁-C₆)-straight alkyl-OR₁₇, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, -S(O)₂-(C₁-C₆)-straight or branched alkyl, or -S(O)₂-Ar; wherein

any alkyl, alkenyl or alkynyl group is optionally substituted with 1 to 3 independently selected halo groups; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally substituted with 1 to 3 substituents independently selected from halo, hydroxy, nitro, cyano, amino, (C₁-C₄)-straight or branched alkyl; O-(C₁-C₄)-straight or branched alkyl, (C₂-C₄)-straight or branched alkenyl or alkynyl, or O-(C₂-C₄)-straight or branched alkenyl or alkynyl;

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally benzofused; with the provisos that:

at least two of R₁, R₂, R₃, R₄, or R₅ is hydrogen;

no more than two of R₁, R₂, R₃, R₄, or R₅ comprises Ar;

at least two of R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen; and

no more than two of R₇, R₈, R₉, R₁₀ or R₁₁ comprises Ar; and

b) a pharmaceutically acceptable carrier, adjuvant or vehicle.

20. The composition according to claim 19, further comprising of this invention comprise a compound an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound.

21. A use of a composition according to claim 19 or 20 for the preparation of a medicament for treating or preventing an IMPDH-mediated disease or condition in a mammal.

22. The use according to claim 21, wherein said IMPDH-mediated disease or condition is selected from transplant rejection, graft versus host disease, an autoimmune disease.

23. A use of a composition according to claim 19 or 20 for the preparation of a medicament for inhibiting viral replication in a mammal.

24. The use according to claim 23, wherein the viral replication to be inhibited is that of a virus selected from orthomyxovirus, paramyxovirus, herpesvirus, retrovirus, flavivirus, pestivirus, hepatotrophic virus, bunyavirus, Hantaan virus, Caraparu virus, human papilloma virus, encephalitis virus, arena virus, reovirus, vesicular stomatitis virus, rhinovirus, enterovirus, Lassa fever virus, togavirus, poxvirus, adenovirus, rubiola, or rubella is inhibited.

25. A use of a composition according to claim 19 or 20 for the preparation of a medicament for inhibiting vascular cellular hyperproliferation in a mammal.

26. The use according to claim 25, wherein said medicament is useful in treating or preventing

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restenosis, stenosis, atherosclerosis or other hyperproliferative vascular disease.

27. A use of a composition according to claim 19 or 20 for the preparation of a medicament for inhibiting tumors and cancer in a mammal.

28. The use according to claim 30, wherein said medicament is useful to treat or prevent lymphoma, leukemia and other forms of cancer.

29. A use of a composition according to claim 19 or 20 for the preparation of a medicament for inhibiting inflammation or an inflammatory disease in a mammal.

30. The use according to claim 29, wherein said medicament is useful for treating or preventing osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma or adult respiratory distress syndrome.

31. The compound of claim 1 or the composition of claim 19 or 20, wherein X is $-N(R_6)-C(O)-Y-$.

32. The compound or composition of claim 31, wherein Y is $-C(R_{12})=C(R_{12})-$.

33. The compound of claim 1 or the composition of claim 19 or 20, wherein Q is $-N(H)-C(O)-O-$.

INTERNATIONAL SEARCH REPORT

In international Application No

PCT/US 99/09005

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | |
|------------------|------------|------------|------------|------------|
| IPC 6 C07C235/56 | C07C217/84 | C07D263/32 | C07C311/21 | A61K31/165 |
| A61K31/135 | A61K31/18 | A61K31/395 | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | <p>CHEMICAL ABSTRACTS, vol. 110, no. 25, 19 June 1989 (1989-06-19) Columbus, Ohio, US; abstract no. 228120q, MULLINK H. ET AL.: "Combined immuno- and non-radioactive hybridocytochemistry on cells and tissue sections:" page 317; column 1; XP002111108 abstract & J. HISTOCHEM. CYTOCHEM., vol. 37, no. 5, 1989, pages 603-609, ---</p> <p style="text-align: right;">-/--</p> | 1,19,20 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

3 August 1999

17/08/1999

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Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/09005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | CHEMICAL ABSTRACTS, vol. 110, no. 1, 2 January 1989 (1989-01-02) Columbus, Ohio, US; abstract no. 3327n, WEBBER D. M. ET AL.: "A quantitative cytochemical assay for osteoclast acid phosphatase activity in fetal rat calvaria." page 309; column 2; XP002111109 abstract & HISTOCHEM. J., vol. 20, no. 5, 1988, pages 269-275, --- | 1,20 |
| Y | WO 97 40028 A (VERTEX PHARMA) 30 October 1997 (1997-10-30) cited in the application claims 1-53; examples 1-14; tables IA-IIIB,III --- | 1-33 |
| Y | PATANI G A ET AL: "BIOISOSTERISM: A RATIONAL APPROACH IN DRUG DESIGN" CHEMICAL REVIEWS, vol. 96, no. 8, 1 January 1996 (1996-01-01), pages 3147-3176, XP000652176 ISSN: 0009-2665 page 3170, column 2; table 48 --- | 1-33 |
| X | DE 838 290 C (NAPHTOL-CHEMIE OFFENBACH) 16 August 1951 (1951-08-16) page 2 --- | 1 |
| X | US 3 064 049 A (ROBERT J. COX) 13 November 1962 (1962-11-13) the whole document --- | 1 |
| X | US 1 935 554 A (ERNEST F. GRETHER ET AL.) 14 November 1933 (1933-11-14) claims 1-11; examples 1-3 --- | 1 |
| X | US 2 025 116 A (HERBERT A. LUBS ET AL.) 24 December 1935 (1935-12-24) claims 9-14; examples 1-4 --- | 1 |
| X | US 4 242 260 A (HASHIMOTO MITSURU ET AL) 30 December 1980 (1980-12-30) column 29 - column 42; example 1; table 1 --- | 1 |
| X | FR 1 584 606 A (EASTMAN KODAK COMPANY) 26 December 1969 (1969-12-26) page 3 - page 4 --- | 1 |
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/09005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|----------|---|----------------------|
| X | CHEMICAL ABSTRACTS, vol. 53, no. 12, 25 June 1959 (1959-06-25) Columbus, Ohio, US; abstract no. 11280a, JUN NISHINO ET AL.: "Azo dyes derived from catechol." page 11280; column 2; XP002111110 abstract & YÜKI GÖSEI KAGAKU KYÖKAISHI, vol. 17, 1959, pages 166-169, --- | 1 |
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| X | CHEMICAL ABSTRACTS, vol. 55, no. 24, 27 November 1961 (1961-11-27) Columbus, Ohio, US; abstract no. 24333c, C. R. BARR ET AL.: "Indoaniline dyes." page 24333; column 1; XP002111112 abstract & PHOT. SCI. ENG., vol. 5, 1961, pages 195-197, --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 108, no. 5, 1 February 1988 (1988-02-01) Columbus, Ohio, US; abstract no. 37339s, KISHIMOTO SATOSHI ET AL.: "Synthesis of anilide derivatives of 1-hydroxy-2-naphthoic acid." page 584; column 2; XP002111113 abstract & KAGAKU TO KOGYO, vol. 61, no. 3, 1987, pages 84-88, --- | 1 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

Int. J. Appl. Inv. No

PCT/US 99/09005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | CHEMICAL ABSTRACTS, vol. 110, no. 24, 12 June 1989 (1989-06-12) Columbus, Ohio, US; abstract no. 214736h, SEBE ION ET AL.: "Organic pigments -AS-RS naphthol derivatives." page 103; column 1; XP002111114 abstract & REV. CHIM. (BUCHAREST), vol. 39, no. 10, 1988, pages 850-851, --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 85, no. 17, 25 October 1976 (1976-10-25) Columbus, Ohio, US; abstract no. 123834n, KEKRE J. S. ET AL.: "Syntheses and biological activity of 1,3-naphthoxazine-2,4-diones." page 636; column 1; XP002111115 abstract & INDIAN J. CHEM., SECT. B, vol. 14B, no. 3, 1976, pages 212-213, --- | 1 |
| X | FRIEDRICH RICHTER: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4th. Edition, Suppl. II, vol. 13" 1950, SPRINGER VERLAG, BERLIN. GÖTTINGEN. HEIDELBERG (DE) XP002111105 page 181, paragraph 6 --- | 1 |
| X | HANS-G. BOIT ET AL.: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4th Edition, Suppl. III, vol. 13" 1973, SPRINGER VERLAG, BERLIN. HEIDELBERG. NEW YORK XP002111106 * page 837, paragraph 4; page 838, paragraph 2; page 2155, paragraph 3 * | 1 |
| X | REINER LUCKENBACH ET AL.: "BEILSIENS HANDBUCH DER ORGANISCHEN CHEMIE, 4th Edition, Suppl. IV, vol. 13" 1985, SPRINGER VERLAG, BERLIN. HEIDELBERG. NEW YORK. TOKYO XP002111107 page 1717, paragraphs 1,2 --- | 1 |
| A | US 5 380 879 A (SJOGREN ERIC B) 10 January 1995 (1995-01-10) cited in the application abstract ----- | 1,20-30 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/09005

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: 1-33 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-33 (Partly)

Present claims 1-33 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples 1 to 5 and the tested compounds (see table 2 of pages 62 and 63 of the description).

Claim 1 contains a list of provisos, which renders the scope of claim 1 unclear; since the scope of the claim is not defined in a positive manner.

In view of the preferred compounds of table 1 (see table 1 p. 17 to 38), it appears that the majority of the compounds are N-phenyl-naphthalenecarboxamide derivatives, having a hydroxy or R₀-substituent in ortho position. The search has therefore been directed to such compounds.

It is stressed, that the incomplete search has revealed a very large number of novelty destroying documents and that it was impossible to cite all of them in the search report.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/09005

| Patent document cited in search report | Publication date | Patent family member(s) | | | Publication date |
|--|------------------|-------------------------|------------|--|------------------|
| WO 9740028 A | 30-10-1997 | US | 5807876 A | | 15-09-1998 |
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| | | CZ | 9803380 A | | 17-02-1999 |
| | | EP | 0902782 A | | 24-03-1999 |
| | | NO | 984917 A | | 23-12-1998 |
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